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ABSTRACT

This report of the Health and Human Services Department Task Force on Alzheimer's Disease addresses nine main areas in a problem-oriented approach aimed at better defining research needs and options as well as training, service, and policy issues relevant to Alzheimer's disease. Individual chapters deal with research in the areas of epidemiology, etiology and pathogenesis, diagnosis, clinical course, treatment, the family, and systems of care. Other chapters concentrate on issues related to the training of research and clinical personnel and educational materials and information dissemination for professionals and the public. Sections in each chapter contain recommendations for research, for training (research and clinical), and for information dissemination. References are listed and an extensive appendix of projects on Alzheimer's disease supported by federal programs is included. (ABB)

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Report of the
Secretary's Task Force on Alzheimer's Disease
U.S. Department of Health and Human Services

September 1984

Alzheimer's Disease

Report of the
Secretary's Task Force on Alzheimer's Disease

Participating agencies:

Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration
National Institute of Mental Health
National Institutes of Health
National Institute on Aging
National Institute of Allergy and Infectious Diseases
National Institute of Neurological and Communicative Disorders and Stroke

Administration on Aging

Health Care Financing Administration

Veterans Administration

September 1984

U.S. Department of Health and Human Services

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Foreword

Fifteen Presidents ago--when William McKinley occupied the White House and the 20th century began--few Americans lived to celebrate their 65th birthday: only 4 percent of the population was 65 or older.

Today, our national longevity has increased by three decades; more than 11 percent of our population is elderly. Older Americans will become 20 percent of our population by the year 2030.

Look at the numbers: 3 million Americans were 65 or older in 1900. Today, that figure has jumped to over 27 million. Tomorrow (in 2030) more than 50 million Americans will live to be 65.

Given the threshold blessing of longer lives, the important question then becomes how healthy, active, and independent our older years will be. Even as the proliferation of medical miracles and ever improving health care have been major contributing factors in this ongoing transformation of our national "profile," too many of our people still fall prey to serious illnesses. None is more terrifying and life altering for the elderly than Alzheimer's disease.

As soon as I became Secretary of Health and Human Services, I determined to upgrade the Department's attack on Alzheimer's disease by mustering the medical and scientific expertise of this Nation in a massive effort to conquer this now incurable disorder that strikes almost two million elderly Americans, causing them and their families so much anguish and suffering.

Dr. Lewis Thomas of the Sloan-Kettering Institute, a noted medical researcher and author, has called Alzheimer's the disease of this century. Both its seriousness and evolving theories as to its causes have begun to spur a new generation of scientific research, bringing exciting promise that this enemy of our older years may be struck down at last.

It seemed to me that our first steps could also be giant steps in the direction of treatment and cure. I therefore assembled a Special Task Force with the assignment of producing an in-depth study of the current state of medical knowledge of Alzheimer's disease and a blueprint that would put the victims, their loved ones, and medical science on the pragmatic and scientific road to progress.

That Task Force, under the direction of Assistant Secretary Edward N. Brandt, Jr., has--magnificently--honored its mandate. Beginning with the commitment, support, and contribution of 10 agency and program heads from across the Department of Health and Human Services and the Veterans Administration, experts, researchers, and clinicians from hospitals and universities throughout our country brought their experience, enthusiasm, and talent to bear on the challenge of Alzheimer's disease.

The Report that follows builds upon scientific consensus and dramatically documents the fruits of an integrated effort. It recognizes and is based on the need for a broad-based approach. Equally important, it presents a detailed plan for the future even as it codifies the considerable current scientific undertakings. There is diverse and extensive research in progress as this Report goes to the printer. The research effort, supported by this Department, is exploring many avenues--from the intricacies of brain tissue changes to how best to assist the family support system. In addition to research, the Report addresses the need to prepare new researchers, to improve the skills of clinicians, and to convey our scientific findings to those who care for Alzheimer's disease patients--the physician, the family, the community.

These are critical areas of investigation and there are others, as well, beyond scientific research, that need to be explored to ease the burden that Alzheimer's disease inflicts on families. The work of this Task Force and the new and continuing efforts ahead in both the public and private sectors can offer ways to translate research results into policy and practical means for improving the quality of life for older Americans suffering from Alzheimer's disease.

In accepting the Report of the Task Force, I recommit myself to the task of unraveling the mystery and the curse of Alzheimer's, a disease that robs us of immense human and intellectual treasure.

When we find a cure for Alzheimer's disease, we--as a people--will release and reap a now untapped harvest of wisdom, insight, and experience from millions of Americans in their golden years.

Margaret M. Heckler

Margaret M. Heckler
Secretary of Health and Human Services

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Executive Summary

President Reagan, in his proclamation of November 1983 as National Alzheimer's Disease Month, pointed out that

> Alzheimer's disease, a devastating disease that affects the cells of the brain, is now regarded as the major form of old age 'senility.' While experts formerly believed that Alzheimer's occurred only in persons under 65, it now is recognized as the most common cause of severe intellectual impairment in older individuals. Presently there is no established treatment that can cure, reverse, or stop the progression of this disorder which is the cause of serious confusion and forgetfulness in about 1.5-2.5 million elderly persons in the United States.

President Reagan indicated further that Alzheimer's disease is associated with a decrease in life expectancy and that it "also deprives its victims of the opportunity to enjoy life and takes a serious toll on its victims' families and friends." The President also emphasized that:

> The emotional, financial and social consequences of Alzheimer's disease are so devastating that it deserves special attention. Science and clinical medicine are striving to improve our understanding of what causes Alzheimer's disease and how to treat it successfully. Right now, research is the only hope for victims and families.

In recognition of the special attention that Alzheimer's disease deserves, Secretary Heckler established the Health and Human Services (HHS) Departmental Task Force on Alzheimer's Disease, which first met in April 1983. The Task Force has been Chaired by the Honorable Edward N. Brandt, Jr., M.D., the Assistant Secretary for Health, DHHS, and has consisted of 10 agency and program heads from across DHHS, along with representation from the Veterans Administration (VA). The Secretary's charge to the Task Force was fourfold:

> coordinating the intensive on-going research already being done at HHS on Alzheimer's disease; creating a mechanism

for sharing information by all programs in the Department serving the elderly; identifying the most promising research avenues to explore; and providing the vehicle for translating that research into policy, programs, and practical means for improving the quality of life for older Americans.

The number of unanswered questions is so great that Federal support of research on Alzheimer's disease was increased from less than $4 million in 1976 to approximately $25 million in 1983. The cause of Alzheimer's disease is unknown, data on its prevalence vary, and it can be difficult to diagnose, since many disorders manifest symptoms mimicking those of Alzheimer's disease. Our lack of understanding of Alzheimer's disease leaves major gaps gaps in treatment, gaps in efforts to assist families of Alzheimer's disease patients, gaps in other systems of care, gaps in the training of research and clinical personnel, gaps in educational materials and information dissemination for the public and professionals, and gaps in the financing of systems of care.

Accordingly, the Task Force Report has addressed nine main areas in a problem-oriented approach aimed at better defining research needs and options as well as training, service, and policy issues relevant to Alzheimer's disease. The nine areas are as follows:

1. Research on epidemiology
2. Research on etiology and pathogenesis
3. Research on diagnosis
4. Research on clinical course
5. Research on treatment
6. Research on the family
7. Research on systems of care
8. Training of research and clinical personnel
9. Educational materials and information dissemination for professionals and the public

Workgroups were formed under the Task Force to focus more intensively on these problem areas. Information from the nine workgroups is contained within the respective chapters of the Task Force Report that elaborate current knowledge, promising research directions, and recommendations on Alzheimer's disease.

The HHS Departmental Task Force on Alzheimer's disease has to date addressed all four points of Secretary Heckler's charge. Through the meetings of the Task Force and its various workgroups, the Task Force members have coordinated ongoing research on Alzheimer's disease in the Department of Health and Human Services (Charge 1); and through the information exchange networks set up, have created ongoing mechanisms for sharing information among the different programs in the Department serving the elderly (Charge 2). This report reflects the delineation and organization of this information; the Appendix lists actual research and training projects supported by the respective programs represented on the Task Force, in addition to service programs funded by the Veterans Administration, thereby facilitating the process of coordination. The sections of the report addressing research on epidemiology, etiology and pathogenesis, diagnosis, clinical course, treatment, the family, and systems of care identify the most promising research avenues to explore (Charge 3). With regard to the fourth charge, the sections on training, and information dissemination offer ways for translating the present results of research into policy, programs, and practical means for improving the quality of life for older Americans with Alzheimer's disease.

The recommendations represent the best judgment of leading authorities on Alzheimer's disease from both inside and outside Government, including agency directors, scientists, educators, and clinicians. The Alzheimer's Disease and Related Disorders Association, a national association of Alzheimer's disease victims and their families with chapters across the United States, provided significant input throughout the deliberations of the Task Force.

In this summary, the recommendations from each of the nine chapters of the Task Force Report are organized in three sections: Recommendations for Research; Recommendations for Training - Research and Clinical; Recommendations for Information Dissemination. Background justification for the three groupings of recommendations below and additional details on them are presented in the body of the report.

The work of the Task Force continues.

Recommendations for Research

The following research areas are recommended as promising directions for future research. They are built upon a foundation of basic and applied research in all the biological, clinical, behavioral, and social sciences and depend upon advances in these fields for their continued growth.

Research on Epidemiology

1. Develop standardized diagnostic assessments for Alzheimer's disease that are suitable for use in field studies.

2. Determine age-specific incidence and prevalence rates of Alzheimer's disease in diverse populations and study the course of illness.

3. Assess a variety of possible risk factors that may be associated with the development of Alzheimer's disease.

Research on Etiology and Pathogenesis

1. Support and enlarge research in order to enhance understanding of the cause(s) of the progression of Alzheimer's disease. Such research would include attention to the etiological impact of chemical deficiencies in the brain, advancing chronological age, genetic abnormalities, atypical transmissible agents, environmental toxins and trace metals, autoimmune dysfunction, and psychosocial trauma and stressors.

2. Encourage existing brain tissue banks to include tissue from Alzheimer's disease patients and from age-matched controls; periodically review to ensure an adequate number of such facilities.

3. Develop animal models of Alzheimer's disease with more precise neuropathologic and biochemical correlates.

Research on Diagnosis

1. Develop international standardized diagnostic research criteria.

2. Develop biological and/or behavioral markers for the early detection of Alzheimer's disease.

3. Undertake longitudinal studies in order to document in a systematic fashion the progression of the disease.

4. Examine cases of serious discrepancy between degree of cognitive deficit and extent of brain impairment.

Research on Clinical Course

1. Develop longitudinal assessment instruments capable of reliably measuring behavioral and biological change over multiple points in time.

2. Investigate factors that hasten or delay the progression of symptomatology.

3. Examine individual differences and variability in severity, rate of deterioration, duration of illness, and capacity for self-care.

Research on Treatment

1. Develop new treatment agents for the cognitive and other

impairments of Alzheimer's disease.

2. Develop new experimental animal models, based on actual neuropathological findings in human populations.

3. Establish more sensitive measures of cognitive, affective, somatic, and other changes for use in drug outcome studies.

4. Develop psychotherapy modalities for the treatment of secondary psychiatric symptoms and syndromes in Alzheimer's disease patients, and devise behavioral interventions for the modification of specific problem behaviors in Alzheimer's disease patients.

5. Evaluate the influence of the environment on Alzheimer's disease patients and collect information regarding the range of behavioral plasticity in patients at different stages of the disease.

6. Study the efficacy of support and self-help groups in ameliorating stress for family members and caretakers.

7. Determine the impact of teaching behavioral management strategies and coping skills to caregivers.

8. Evaluate which patient behaviors are significantly associated with the family's desire to institutionalize.

Research on the Family

1. Evaluate those factors that aid the family in the early recognition of symptoms, the decision to seek medical care, and the decision to assume and play a primary caregiver role.

2. Identify the most effective coping strategies and interventions used by caregivers; and identify the kinds of information, education, support, and treatment that best reinforce or increase coping abilities of families with Alzheimer's disease members.

3. Explore innovative social support systems for those Alzheimer's disease patients who do not have any family members available for assistance.

Research on Systems of Care

1. Study the range of community and institutional services relevant to Alzheimer's disease patients in terms of their design, staffing, timing of use during the progression of the

disorder, mix and coordination with other services, and costs. The National Center for Health Services Research (NCHSR), in addition to the programs represented on the Task Force, should be considered in this effort.

2. Sponsor jointly state-of-the-art conferences and workshops with broad dissemination of proceedings, coordinating such efforts with programs represented on the Task Force along with NCHSR.

Recommendations for Training: Research and Clinical

The Task Force recognizes that adequate training of investigators and academic leaders in all appropriate disciplines should be a high priority in order to advance research relevant to Alzheimer's disease and to conduct the extensive teaching needed by all professionals who have roles in diagnosing, treating, and caring for persons with dementia.

In November 1983, Assistant Secretary for Health Brandt established an interagency geriatric training committee within DHHS (the HHS Ad Hoc Committee on Enhancement of Training in Geriatrics and Gerontology), with representatives from the Veterans Administration and other Federal programs, for purposes of coordinating and planning an overall geriatric training strategy that includes attention to research training and clinical training needs in the area of Alzheimer's disease.

The Task Force is reviewing the findings and recommendations of this interagency geriatric committee in order to better coordinate training initiatives across the Department and the VA relevant to Alzheimer's disease.

Recommendations for Information Dissemination

1. The information offices of the Department and other Federal agencies represented on the Task Force should distribute all information materials on Alzheimer's disease developed by each Federal program.

2. The Task Force should oversee the preparation of two new pamphlets on Alzheimer's disease--one addressed to the practitioner, the other addressed to the family.

3. Voluntary agencies should be encouraged to assist in the processes of disseminating information and developing new educational materials as addressed in the aforementioned two recommendations.

Special Financing Recommendation

Removing Limitations on Services Provided Outside of the Hospital Setting

Current Medicare statute limits medically appropriate physician services provided outside of the hospital setting for patients with Alzheimer's disease when coded as a mental disorder. The Department should clarify that, except for psychotherapy, physician treatment services for patients with Alzheimer's disease and related disorders are not subject to the $250 limitations. In other words, in determining whether services for these patients are subject to the limit, the nature of the physician's service is the deciding factor, not the diagnostic code. Therefore, physician treatment services provided outside the hospital setting for patients with Alzheimer's disease and related disorders coded 290.X (in DSM-III and ICD-9) should be reimbursed in the same manner as services for Alzheimer's disease coded 331 (ICD-9).

CURRENT KNOWLEDGE, PROMISING DIRECTIONS, AND RECOMMENDATIONS

Chapter 1

Research on Epidemiology

Current Knowledge Base

Demographic Trends

To date, no risk factors have been definitively associated with Alzheimer's disease, and only advanced chronological age itself appears to correlate clearly with the development of this disorder. The impact of the age factor is ominous, however, since international demographic trends indicate how very rapidly the population most susceptible to Alzheimer's disease has increased during this century and how swiftly it will continue to grow. The elderly population in the United States has increased more than eightfold, from approximately 3.1 million people aged 65 and over in 1900 to 26 million in 1980. This represents a rise from 4.1 to 11.3 percent of the total population. The U.S. Bureau of the Census projects that the number of persons over age 65 will reach 33.5 million to 36.6 million by the year 2000, accounting for about 13 percent of the total population. Further, the number and proportion of Americans 65 and older are forecast to continue increasing as children from the post-World War II baby boom age, reaching a peak of approximately 58.5 million (20 percent) by the year 2025. Current estimates suggest that one-third of the entire population in the developed countries will survive to at least 80 years of age, when the risk of having Alzheimer's disease increases to about 20 percent.

Incidence and Prevalence

In order to determine better the true magnitude of the problem, epidemiologists have sought to assess the incidence and prevalence of Alzheimer's disease among groups of individuals categorized according to specified clinical and demographic characteristics. A serious problem in establishing the incidence, in particular, is the difficulty in recognizing the early stages of Alzheimer's disease. For the most part, estimates of the incidence of dementia have been few and of uncertain comparability. Kokmen and Schoenberg have reported an annual incidence of 110 new cases per 100,000 among the residents of Rochester, Minnesota, over 29 years of age. Their figures were based on clinically restrictive criteria applied to individuals whose condition had been recognized and documented by physicians in medical facilities in that area over a 5-year period. In a study carried out in Sweden, Akesson estimated the annual incidence of "senile psychosis" among persons age 60 and older as 380 per 100,000. His estimate for the incidence of dementia due to "severe arteriosclerotic psychosis" (a term of uncertain meaning in view of current knowledge) was 520 per 100,000 in the same population. While there is no clear indication that rates have changed over time, obviously, with the increasing number of persons surviving into old age, the absolute number of cases is increasing rapidly.

The possibility that changes in reported mortality and prevalence of dementia might actually reflect a changing incidence within a single community was considered by Gruenberg with reference to a study carried out in Southern Sweden between 1947 and 1957. He concluded that improvements in medical treatment had increased the duration of illness and (thereby) the point prevalence, but that these did not indicate a true increase in disease incidence. It seems generally accepted that the incidence of dementia in the elderly is, in fact, fairly constant over time and over large geographic areas.

Estimates of the prevalence of dementia from population studies in Northern Europe have ranged from 3.9 to 21.6 percent (severe dementia, 1.3 to 6.2 percent; mild impairment, 2.6 to 15.4 percent) among the elderly (Bollerup 1975; Broe, Akhtar, Andrews, Caird, Gilmore, and McLennan 1976; Essen-Moller, Larsson, Uddenberg, and White 1956; Kay, Bergmann, Foster, McKechnie, and Roth 1970; Kay, Beamish, and Roth 1964; Nielson 1963; Primrose 1962). A recent study conducted in Copiah County in rural Mississippi resulted in an estimate of 1 percent for severe dementia among county residents age 40 and older, climbing to a 7-percent prevalence among residents age 80 or older. Severe dementia was found to be equally common in blacks and whites. These figures derive from stringent inclusion criteria limited to severe cases. In Akesson's study, the age-specific prevalence of severe dementia at age 80 and above was 4.8 percent. Less restrictive criteria have resulted in higher age-specific prevalence figures, such as 12.6 percent and 22 percent among persons age 80 and older. In general, there appears to be a ten- to twentyfold increase in age-specific prevalence between the ages of 60 and 80, exceeding 20 percent by 80 to 85 years. Moreover, these figures are generally agreed to be underestimates of the true prevalence. Age-specific prevalence may level off or even decline after age 80, suggesting an age range of maximum incidence with fewer new cases in the extremely long lived.

Life Expectancy and Disease Correlates

Alzheimer's disease may be associated with reduced life expectancy. Data from Rochester, Minnesota, demonstrate a lower survival rate for those individuals with Alzheimer's disease, beginning 3 years after the diagnosis was established. It is not clear whether the disease itself plays a direct role in shortening life, or whether this shortening results from the poor self-care associated with the intellectual deterioration that characterizes the illness. Findings from several case-control studies of Alzheimer's disease have demonstrated associations with a history of head injury, with the presence of Down's syndrome, and with the manifestation of an autoimmune disorder.

Epidemiologic studies in Guam, New Guinea, and parts of Japan indicate similar neuropathologic changes in the brains of Alzheimer's patients and victims of amyotrophic lateral sclerosis (ALS) and parkinsonism-dementia syndrome. Analyses of garden soil and drinking water in these three areas plagued by high incidences of ALS and dementia show low levels of calcium and magnesium and unusually high levels of aluminum. This suggests a possible link between diet, hormonal changes, and the presence of environmental toxins in the etiology of Alzheimer's disease.

Problems in Case Ascertainment Methodology

The actual case ascertainment procedures used in epidemiologic studies of Alzheimer's disease often incorporate serious biases that limit accuracy. For example, at autopsy, in some studies, as many as 30 to 40 percent of elderly patients with clinically diagnosable dementia do not manifest the pathologic changes characteristic of Alzheimer's disease. Therefore, in surveys and in most clinical studies, the specificity of the diagnosis is often uncertain.

Typically, epidemiologic studies require two-stage assessment procedures for identifying likely cases of Alzheimer's disease. While screening instruments are used to determine cognitive functioning in large population samples and in cross-sectional studies, it is often especially difficult to determine whether the identified impairment in cognition and function has always been present, or whether it represents a significant decline over time. Once those with evidence of deterioration have been identified, a clinician can then perform a detailed examination in order to differentiate those with other known causes of dementia from those with Alzheimer's disease. One difficulty arises because the diagnosis of Alzheimer's disease can only be made by exclusion and many medical conditions are associated with dementia or mimic Alzheimer's disease, making it time consuming and expensive to rule out all competing causes of cognitive impairment.

In addition, all the procedures used to establish disease frequency have their own sets of methodologic problems. Mortality data are generally not useful in dementia research because of extensive underreporting. The validity of prevalence estimates depends on several factors relating to the identification of all cases in the population. Approaches that depend upon recognition of dementia during conventional medical contacts are of unacceptably limited utility both because of the nature of the condition and because of the many cultural, social, and behavioral factors that cause some patients and their families to seek early professional attention and others to delay or avoid physicians and other caregivers. For example, the individual who lives with his family in a sheltered environment is less likely to come to medical attention than another who does not have these advantages, or vice versa. A further difficulty comes from the variability of the degree of impairment, with individuals slipping into and out of states of impaired cognitive functioning. This may lead to underdiagnosis or to ambiguity of the diagnosis. Varying education, social class, and language backgrounds also profoundly influence the expression and/or recognition of cognitive disability.

Ongoing Federal Studies

A number of epidemiologic studies of dementia in late life are currently underway with Federal support. Three community studies of elderly populations are being conducted--in New Haven, East Boston, and Iowa--for longitudinal followups of the population over 65 (supported by the National Institute on Aging--NIA). In East Boston, 100-200 subjects identified as having Alzheimer's disease will be matched to controls and followed for 5 years to determine the course of natural history of the disease. Followup studies of aging subjects first seen in the HANES I survey (conducted by the National Center for Health Statistics--NCHS) and the Framingham cardiovascular study (sponsored by the National Heart, Lung, and Blood Institute--NHLBI) are also being conducted, in collaboration with NIA. These studies will allow documentation of prior risk factors, determination of course of illness, and differentiation of Alzheimer's disease from other major causes of dementia.

In the context of the Epidemiological Catchment Area (ECA) Program (initiated and supported by the National Institute of Mental Health--NIMH), five sites across the country have been sampled on a probability basis. About 3,000 household and 500 institutional residents, living in a designated community with a population base of about 200,000, have been examined. At all sites cognitive impairment has been evaluated by the mini-mental status examination (MMSE). Supplements to the ECA program from NIA and from the NIMH Center for Studies of the Mental Health of the Aging have expanded the Baltimore and New Haven ECA samples by adding 1,000-2,000 elderly household residents. As a supplement to the Baltimore study, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) has funded a second-stage clinical examination of subjects with low MMSE scores to differentially determine the presence of specific types of dementia. Findings from these studies are not yet available.

NINCDS is supporting epidemiologic studies in Copiah County, Mississippi; in Rochester, Minnesota; and in Israel. In Mississippi, a total population survey of 28,000 county residents and institutionalized patients, using a two-stage design of screening and clinical examination, revealed that severe dementia was equally common in blacks and whites. There was a strong positive association with increasing age and a weak association with being female. In Rochester, a life-table analysis from medical records demonstrated a lower survival rate for those with dementia generally and those with Alzheimer's disease particularly, beginning 3 years after the diagnosis was established. The studies using an Israeli registry of neurologic patients younger than 60 revealed an association between increasing age and Alzheimer's disease as well as a higher rate for females and for some ethnic groups.

Future Research Directions

Serious epidemiological inquiries concerning Alzheimer's disease have had formidable difficulties in establishing an unambiguous ante mortem diagnosis of the disease. Accordingly, a primary need is for the specification of systematic, operationalized diagnostic research criteria, linked to the development of standardized screening measurements, structured interviews, and psychometric assessments, which can achieve national and international acceptance through careful testing and followup. These must include instruments that can be used for field testing, others that can be used in hospitals and clinical settings, and yet others that are useful for following patients over time. Moreover, an acceptable rating score is needed that reliably quantifies severity over a range of clinical signs and symptoms. In the development of these measures, it would be profitable to anchor all clinical instruments to standardized neuropathological diagnoses. Ultimately, such integration of clinical and laboratory efforts with epidemiologic approaches will yield more precise and reliable information.

In addition, case-control studies, studies of incidence in varied populations, longitudinal followups of the natural history and course of the disorder, and evaluations of risk factors are all urgently needed. Considering the magnitude and importance of Alzheimer's disease, our current meager knowledge of these issues must be expanded rapidly.

Recommendations for the Development and Implementation of Research

Accordingly, the following recommendations are set forth in order to develop collaborative national and international research efforts in the epidemiology of Alzheimer's disease. These include recommendations:

To develop and evaluate standardized diagnostic assessments for Alzheimer's disease that are suitable for use in field studies.

1. More precise diagnostic criteria to differentiate types of dementia, especially Alzheimer's disease, should be formulated for DSM-IV and ICD-10. These should be tested in studies of differential diagnosis.

2. An assessment procedure may consist of a two-stage process, with screening using a simple measure to detect cognitive impairment followed by examination by an experienced clinician for differential diagnosis.

3. Supplementary procedures for more detailed neuropsychological assessment could be developed to allow clinicopathological correlation in followup studies that continue to autopsy.

4. Special problems include the need to demonstrate cognitive decline over time and the ability to assess those whose decline begins at a high intellectual level, those who have had minimal education, and patients from diverse cultural settings.

5. Efforts to develop early screening procedures for the diagnosis of Alzheimer's disease using automated, comprehensive assessments of cognitive and neurophysiological functioning should be undertaken.

6. To allow for better understanding of the relationship between clinical and neuropathological changes, clear criteria and standards for post mortem pathology diagnoses (that do not depend on clinical history) need to be developed.

To determine age-specific incidence rates, especially to identify variations by sex, race, geography, social class, etc., and to study the course of illness.

1. Subjects in a variety of locations, including foreign countries, should be included.

2. The studies could take advantage of preexisting cohorts formed initially to study other problems (e.g., as is already being done in the Framingham samples, NIMH Epidemiological Catchment Area samples, and HANES followup).

3. If the medical record information is adequate, patient populations in large medical practices may be convenient samples to study (e.g., VA system, Kaiser, Group Health Association plans).

4. Studies to determine possible differences between early-onset and later-onset forms of the disease should be conducted.

To examine a variety of risk factors using case-control, family-pedigree, and other designs.

1. Case-control designs could be used to assess risks for such factors as drug and alcohol use, history of head trauma, and environmental or occupational exposures.

2. Patterns of inheritance, relation to conditions such as Down's syndrome, and heterogeneity of the illness may be clarified by studying familial cases of Alzheimer's disease.

3. If etiologic hypotheses related to slow viruses, immunologic status, or central nervous system (CNS) cholinergic activity can be assessed with field measurements, these questions can be examined as well. Development of assessment procedures based on biochemical, immunologic, electroencephalographic (EEG), or nuclear magnetic resonance (NMR) techniques should be pursued to see if these can be applied in epidemiologic studies as well as clinical studies.

4. A case-registry, especially for those with early onset or with familial clustering, should be maintained to allow investigation of less common conditions.

5. Cases should be followed through post mortem examination, and tissue banks for brain and other organ materials should be further developed using well-specified criteria for selecting specimens from controls and from selected cases of particular interest. An age-stratified series of autopsies on accident and trauma victims and on other nonhospitalized decedents should be undertaken.

International studies, particularly to determine incidence, prevalence, and risk factors and to develop standardized clinical and field instruments, are urgently needed. These recommendations could be implemented through the collaborative establishment of clinical epidemiology research centers on the part of the National Institutes of Health (NIH), the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), the VA, and the World Health

Organization (WHO). WHO has set the epidemiology and diagnosis of Alzheimer's disease as one of its major priorities in the next decade.

Issuing grant solicitations for both individual research projects and for center projects is an effective way of implementing these approaches. The sponsoring of conferences to exchange findings and help formulate experimental approaches would also be highly useful, together with special incentives for the research training and development of needed scientists and clinicians skilled in epidemiologic methods.

Chapter 2

Research on Etiology and Pathogenesis

Current Knowledge Base

In search of the elusive cause of Alzheimer's disease, new hypotheses are being vigorously tested in a growing number of investigations. These studies are focusing on etiological factors as diverse as chemical deficiencies, immune dysfunction, slow viruses and unconventional agents, toxins, trauma, and genetic abnormalities. Support is increasing for the observation that some Alzheimer's cases appear to have an autosomal dominant pattern. While no other definitive findings have emerged regarding the cause or causes of Alzheimer's disease, much has been learned regarding its pathogenesis and the cellular and chemical events associated with its development.

The Cholinergic Hypothesis

The hallmarks of Alzheimer's disease include selective neuronal death and the presence of neurofibrillary tangles and neuritic plaques. Certain populations of neurons have been shown to be particularly affected, most strikingly those found in the cholinergic, noradrenergic, and somatostatin systems. The most intensive studies in recent years have focused on the cholinergic system. Many investigators have confirmed the presence of a profound decline in the activity of the enzyme choline acetyltransferase (CAT) in the brains of Alzheimer's disease patients. CAT is a key ingredient in the chemical process which produces acetylcholine, a neurotransmitter involved in both learning and memory. Significant associations between this change in neurochemical activity, changes in memory and cognition, and changes in the number of neuritic plaques have been repeatedly documented.

Until recently, the source of cholinergic innervation to the cerebral cortex was unknown. The anatomical site in the brain for production and regulation of acetylcholine has now been identified in a group of neuronal cell bodies, located in the base of the forebrain, in an area known as the nucleus basalis. Selective damage of this area of the brain reproduces in experimental animals the chemical abnormalities in the cerebral cortex observed in Alzheimer's disease. This work has spurred further interest in the development of more useful and precise animal models of Alzheimer's disease. Moreover, post mortem examination of the brains of Alzheimer's disease patients has revealed that these neurons do, in fact, die off selectively. While the acetylcholine-releasing neurons in the nucleus basalis clearly do not represent the only neurotransmitter system affected in Alzheimer's disease, they appear to be the most consistently and severely damaged neuronal population identified thus far. The most prevalent types of treatment studies are based on the hypothesis that augmentation of acetylcholine neurotransmission in the brain may lead to the reduction or amelioration of the symptoms of Alzheimer's disease (see chapter on treatment).

Age of Onset: One Disease or Two?

The issue as to whether Alzheimer's disease is one disease entity or two--with an "early" form (i.e., onset before age 65) and a "late" form (onset in later years)—remains to be resolved. Those who argue that these forms vary only in age of onset claim there are no significant differences clinically and histopathologically between them and that, therefore, they should be considered one entity. Rigorous data do not exist that would support or deny that the etiology, pathogenesis, and natural history of the early form are indeed identical with that of the later form. Not uncommonly the natural course of the disease in younger patients tends to be more malignant. Etiologic research may be better served if scientists do not conclude that this question is already answered.

Heritability

Ongoing studies are also evaluating other hypotheses regarding the cause and progression of Alzheimer's disease. For several decades, research on Alzheimer's disease has hinted that in either its early-onset or later-onset form the disease might be hereditary. In the handful of studies on genetic influence, researchers have found an increased incidence of Alzheimer's disease among parents and siblings of victims. Some studies show a slight increase; others show a considerable one over the occurrence of Alzheimer's disease in the general population. Practically no data are available on risk to children of affected parents. Although a significant clustering of cases of Alzheimer's disease has been demonstrated in some families, no consistent pattern of genetic transmissibility has yet emerged, except in an uncommon dominantly inherited form in which the disease often begins at a younger age. Although the clinical observation that Alzheimer's disease of later onset also occurs in family clusters may be valid, longevity also appears to have a familial distribution. Families with longevity would naturally have more members in the more highly susceptible age range, and hence the impression would be conveyed, correctly or falsely, of a genetic factor in the etiology of Alzheimer's disease. Recent studies of the families of autopsied patients with Alzheimer's disease of early and later onset have disclosed an increased frequency of Down's syndrome in close relatives. The data at present suggest that this association is much stronger when the Alzheimer's disease appears in its presenile form.

Transmission of an Unconventional Agent

The possibility that a slow-acting virus or other unconventional agent is the cause of Alzheimer's disease is based in part on the demonstration of transmissibility of two rare kinds of dementia, Creutzfeldt-Jacob disease and Kuru. The observation that neuritic plaques with amyloid are encountered primarily in Alzheimer's disease, Kuru, Creutzfeldt-Jacob disease, Gerstmann-Straussler syndrome, natural scrapie in sheep and goats, experimental scrapie in mice, and chronic wasting of mule deer, all of which, except for Alzheimer's disease, are transmissible, tends to support this suggestion.

Scrapie, for example, which is a CNS disease of goats and sheep, has been studied as a model for dementing disorders in humans due to slow-acting infectious agents. It has been suggested that animals with scrapie are infected by a small infectious particle containing a protein for which the name "prion" has been coined. While this work remains to be confirmed, it offers a new concept which may be helpful in establishing the etiology of Alzheimer's disease. No present evidence suggests that Alzheimer's disease is contagious through ordinary contact with afflicted persons.

Environmental Toxins and Trace Metals

Evidence of excess accumulation of aluminum within the neurons harboring the classic neurofibrillary tangles of Alzheimer's disease has led some scientists to speculate that aluminum and other trace metals may somehow play a role in the development of the disease. The role of aluminum, however, is far from clear, since those with the greatest exposure to aluminum, such as aluminum workers and individuals on renal dialysis, do not develop neurofibrillary tangles nor Alzheimer's disease. Scientists are still uncertain as to how aluminum actually gains access to the brain. The etiological role of environmental toxins in the pathogenesis of Alzheimer's disease remains unproven and controversial.

Other Factors

A number of other factors have been hypothesized as playing a role in the etiology or pathogenesis of Alzheimer's disease. These enjoy less support than the foregoing but cannot be eliminated from consideration. They include immunological predisposition or changes, chromosomal abnormalities, trauma, alterations in the blood–brain barrier, deficits in brain glucose metabolism, deficiencies in neurotropic hormones, and changes in the regulation and transport of cellular calcium.

Psychosocial Concomitants

Research has not demonstrated that psychosocial antecedents or concomitants (e.g., environmental stressors, depressive states, alcoholism, obesity, smoking, diet, medical care, socioeconomic status, or early life experiences) contribute to the cause or exacerbation of Alzheimer's disease. In general, clusters of cases with common exposures or occupations have not been reported. An exception to this is found among prize fighters who develop a syndrome, dementia pugilistica, which shares a few features with Alzheimer's disease, including dementia, brain atrophy, and neurofibrillary tangles. Studies of trauma may also provide a clue to the cause and/or development of late-life dementia. Other exceptions are the Chamorros of Guam and the Japanese on the Kii Peninsula who suffer from ALS and parkinsonism–dementia syndrome. They differ from their unaffected neighbors in that the mineral content of their water is lower in calcium and magnesium but higher in aluminum, silicon, and other minerals.

Finally, the etiological significance of advancing chronological age, the only established risk factor in Alzheimer's disease to date, has yet to be systematically understood and clarified.

In the past several years, researchers have been able to definitively rule out a number of earlier etiological hypotheses, including the notion that Alzheimer's disease is caused by hardening of the arteries or lack of oxygen to the brain. This in itself is an important step forward. In summary, while the cause of Alzheimer's changes in the brain is not presently known, several viable theories are currently under investigation. Although some are more persuasive than others, none can be viewed as proven.

Future Research Directions

At present, only a few laboratories are rigorously investigating the scientific opportunities identified above, and the gaps in knowledge remain quite vast.

Etiological Hypotheses

Every effort should be made to sustain and enlarge research in order to further enhance understanding of the etiology and pathogenesis of Alzheimer's disease. Such research would include attention to the etiological impact of a broad range of variables.

Chemical Deficits in the Brain

In the immediate future, research will probably continue to focus on areas of the most rapid progress, such as cholinergic and other neurotransmitter deficits and their anatomic substrates in Alzheimer's disease. Quantitative and correlative clinico-anatomical studies should be continued in order to determine as precisely as possible which neuronal populations are most susceptible to the disease process. Further exploration of the cholinergic hypothesis for this disease by correlations of cell counts with choline acetyltransferase activity by age and by clinical status should also be undertaken. Other cholinergic regions of the brain should be studied to establish whether or not all central cholinergic neurons are affected. Possibly the various basal nuclei are quite different chemically, and a clue to the primary degeneration might be obtained by chemical mapping of this region. In this respect, innovative use of radio-labeled tracers in positron emission tomography (PET) scanning of Alzheimer's disease patients to measure disordered cerebral metabolism, receptors, etc., should be encouraged. Moreover, as yet undiscovered neurotransmitters may play a role in Alzheimer's disease. In addition, the intraneuronal neurofibrillary changes need to be characterized completely. This may provide leads to understanding their origin and ultimate impact on cell function.

The components of the neuritic plaques, their interrelationships, and their evolution also need to be extensively investigated. Is the neuritic plaque causally related to axonal degeneration and to cell loss in the basal forebrain nuclei? The cell loss is a most critical finding, and its cause should be investigated. Studies should be encouraged of the etiology and pathogenesis of amyloid fibers by identifying the cell(s) responsible for amyloid production, determining the molecular basis for "turning on" the amyloid producing cells, investigating the role genetics plays in amyloid formation, and determining the relationship between neuritic pathology and amyloid fiber formation.

Studies should be supported of the etiology and pathogenesis of paired helical filaments, including the definition of the origin of the constituent proteins and the conditions of their assembly and disassembly.

Advancing Chronological Age

Further research is needed on the role of the biological mechanisms of aging in the pathogenesis of Alzheimer's disease. Why does the incidence of Alzheimer's disease increase with age? What are the age-related changes in neuronal membranes, axonal transport, immunological mechanisms, neuropeptides, and neurotransmitter systems that might permit expression of Alzheimer's disease and under what circumstances?

Genetic Abnormalities

Genetic studies of Alzheimer's disease should be continued until consensus is reached about the genetic contribution to this disorder. Much more widespread genetic analysis must be carried out on an epidemiologic basis in order to better define the real risk of individuals in any age group. These studies must be carefully conducted and the diagnosis of Alzheimer's disease confirmed by autopsy in as many cases as possible. Special efforts are needed in order to attempt to identify a possible genetic basis for familial Alzheimer's disease. Genetic studies focused on the difference in incidence between the early-onset and later-onset forms may shed light on whether or not Alzheimer's disease is a unitary disorder.

Atypical Transmissible Agents

The possibility that Alzheimer's disease may be due to an atypical transmissible agent should not be wholly neglected, despite the failure up to now to demonstrate convincingly the presence of such an agent. Those most likely to be helpful in this question would be workers in the forefront of virology-molecular biology. Scrapie should continue to be used as a model for the study of the events that lead to neuritic and amyloid plaque formation. In addition, the nature of scrapie-induced alterations in the blood/brain barrier could also be used as a model of barrier changes in Alzheimer's disease.

Environmental Toxins and Trace Metals

Additional studies should be carried out in order to document the quantity and status of aluminum within the brains of Alzheimer's disease patients and controls. Similar studies in older patients with Down's syndrome are also suggested. Naturally occurring and experimental models for Alzheimer's disease should be further explored, such as attempts to induce the histopathological changes encountered in the Chamorros and in primates by manipulation of their mineral intake.

Autoimmune Dysfunction

More systematic investigations should be carried out, mapping the nature and association of systemic autoimmune disorders with the onset of Alzheimer's disease.

Psychosocial Trauma and Stressors

More information is needed regarding putative precipitating factors, such as physical or emotional trauma, surgery, and/or other sociocultural stressors. Researchers should not ignore the role of family structure and relationships, psychological functions, health practices, living environments, and other socioeconomic factors.

Brain Banks

It seems most likely that any investigations of Alzheimer's disease will need to make use of suitably preserved human brain tissues, obtained by biopsy or at autopsy. The role of brain banks assumes particular importance in long-range investigations of the kinds of questions that must be asked about Alzheimer's disease. The value of these tissues is tremendously enhanced when derived from patients whose neurological and mental status are known in detail and who had valid psychometric and psychological assessments made during life. The need is not only for well-documented cases of Alzheimer's disease (in which the diagnosis has been established by standard histopathological criteria), but also for material from people of the same age groups without neuropsychiatric disease (verified by autopsy) and from patients with other neurological and psychiatric disorders. Such tissue collections, which are expensive to maintain and to administer, should be actively supported. These tissues must be freely available to qualified investigators.

The interest in the academic community and the Government funding agencies and the proliferation of Alzheimer's support groups across the country provide the opportunity for a collaborative effort to acquire brains from patients with this disease. In keeping with this, the study of Down's syndrome and its relationship to Alzheimer's disease should also be pursued. Especially to be supported are carefully performed chromosomal studies in correlation with the clinical expressions of dementia and structural features of this disease found at autopsy. A bank of Down's brains would be invaluable, especially if karyotypes had been done on the patients.

Animal Models

Animal models of Alzheimer's disease, which contain more precise neuropathologic and biochemical correlates to the condition in humans, should be developed.

Recommendations for the Development and Implementation of Research

It is absolutely essential to support and enlarge the base of fundamental neuroscience and behavioral science research as it relates to Alzheimer's disease. The training of new investigators is another essential component in this strategy. The etiology of Alzheimer's disease is obscure, and relatively little is known regarding its pathogenesis. It is still too early to identify the specific areas of research that will provide the critical information about etiology of the disease.

Some of the support for basic research should properly be provided in the context of financially stable research centers devoted to the long-term clinical and basic study of the Alzheimer's disease population and those at risk. Such patients must be studied behaviorally, chemically, and physiologically with the newest technologies. Multidisciplinary and cross-disciplinary fundamental approaches are needed by investigators with open minds, willing to take conceptual risks in order to identify clues which may prove insightful. Verification of the diagnosis and intensive study of the brains of those patients who were thoroughly evaluated during life are essential.

Such research centers should serve also as the training ground for new investigators (e.g., in neuroscience, behavioral science, genetics, immunology, or infectious diseases) in order to increase the currently small critical mass of scientists. The importance of providing stable support to these investigators over a prolonged period cannot be overemphasized. Support should be provided to investigators on a competitive basis, through interagency collaborative efforts.

Chapter 3

Research on Diagnosis

Current Knowledge Base

Problems in Diagnosis

At the present time, the definitive diagnosis of Alzheimer's disease is based upon the observation at autopsy or biopsy of large numbers of neurofibrillary tangles and senile plaques in the cerebral cortex of clinically demented individuals. The clinical diagnosis is made in progressively dementing individuals in whom other, known causes for the cognitive and memory impairment have been excluded. The tools used typically include, but are not limited to: history, including activities of daily living; physical examination; neurological and psychiatric evaluations; mental status examination and psychometric tests; laboratory studies of blood and urine; and computerized axial tomography (CT).

Nevertheless, even with the best information available, it is often difficult to distinguish the specific Alzheimer's disease patient, particularly early in the course of the disease, from multi-infarct dementia, depression, or other functional states.

The DSM-III Criteria and Discrepant Cases

According to the criteria specified in DSM-III (*Diagnostic and Statistical Manual of Mental Disorder III* of the American Psychiatric Association), Alzheimer's disease can be viewed as consisting of three components: a) memory and other cognitive impairment—the core features of dementia; b) functional and structural impairment of the brain; and c) behavioral manifestations that affect the patient's ability for self-care, interpersonal relationships, and adjustment in the community. While these three components are grossly related, they do not closely parallel each other. For example, in some cases, memory and other cognitive impairment is rather severe, although there may be minimal or no evidence of other cerebral dysfunctions. In other cases, the reverse may happen—there is little memory and cognitive impairment in the presence of significant manifestations of brain dysfunction. Tomlinson postulates that changes not easily identified and quantifiable, such as neuronal loss, may account for those cases of dementia that show no identifiable pathognomonic pathological lesions. He suggests that the extent of intellectual impairment is determined by the degree of aging changes, such as the number of neurons lost, and the location in the brain of these and other characteristic changes.

Although the severity of cognitive deficit is usually correlated with the severity of brain changes, there are discrepancies among these variables. Moreover, significant discrepancies are often found among findings derived from CT scans, mental status examinations, and diagnostic interviews by clinicians.

Psychological Tests and Clinical Neuropsychiatric Assessment

Numerous studies have revealed significant correlations between performance on mental status questionnaire-type tests and level of education. Like other psychological tests of cognitive function, the MSQ, SPMSQ, the Mini-Mental, and others are influenced by factors such as social class, motivation, attention, communication problems, emotional disorders, physical health, and reaction to the test situation itself. Such factors may distort assessment of cognitive status and thus undermine the sensitivity and validity of the test as an indicator of a dementing process.

Similarly, validity of the clinical diagnosis of Alzheimer's may be undermined by such factors as inadequate investigation and history taking, poor reporting of symptoms on the part of the patient or an informant, and atypical presentations of the disorder. Results from the U.S.-U.K. Cross National Study of Diagnosis revealed, for example, that psychiatrists in New York frequently formulated a diagnosis of dementia in elderly patients even when the symptom patterns, psychological tests, and outcomes were not characteristic of a dementing process.

Since all available instruments used in assessing dementia are less than perfect, and the sensitivities vary with circumstances, no single approach can be regarded as sufficient. Caution must be advised when accepting the results obtained by one type of indicator while dismissing discrepant findings by other instruments. Psychological tests may be administered more universally across locations than neuropsychiatric examinations, but they are generally not as valid in a highly skilled clinical evaluation. In pointing to the differences in prevalence rates for severe dementia reported in various community surveys (from 1 to 7.2 percent for severe dementia), Kay suggests that the discrepancies are mainly due to the variability in method of evaluation and criteria for diagnosis.

The Clinical Neurological and Psychiatric Evaluation

Neurological and psychiatric evaluations of suspected Alzheimer's victims must be performed by skilled clinicians with expertise in the organic disorders. Both the history and clinical evaluation should provide information that will support or exclude the diagnosis of Alzheimer's disease. These examinations must include an assessment of higher cerebral functions such as memory, language, praxis, and visuospatial behavior. Early in the course of dementia, only one or two cognitive functions may be impaired. With progression, multiple other cognitive functions will fail. Affective state, anxiety level, and delusional beliefs should also be examined.

Although functions other than cognition are usually spared early in the development of Alzheimer's disease, nonspecific frontal lobe signs such as a snout reflex or jaw jerk occasionally may be encountered. Even less commonly, other signs, such as hypertonia, paratonic rigidity, and gait disturbances may be found fairly early in the course of the illness. Many neurological and psychiatric findings in demented patients, when present, suggest a diagnosis other than Alzheimer's disease, e.g., affective psychosis, papilledema, hemiparesis, ataxia, and lower motor neuron dysfunction.

With progression of the disease, the symptoms and signs worsen and become increasingly evident and disabling. These include, *inter alia*, affective disorders, apathy or agitation, psychotic behavior, slowing of movement, loss of communicative ability, and incontinence.

Laboratory Studies

Complete blood and urine studies should be performed in order not to miss treatable causes of dementia such as B_{12} deficiency. Other more selective studies may be helpful. A substantial number of Alzheimer's disease patients have abnormal electroencephalograms. The CT scan, while its use as a positive diagnostic tool in Alzheimer's disease is of uncertain value, is essential in the exclusion of other disorders such as subdural hematoma or brain tumors. Examination of cerebrospinal fluid may also be warranted as an exclusionary tool and is likely to be important in research studies. Information important in Alzheimer's disease patients can also be derived from studies of regional cerebral blood flow (CBF), evoked potential testing and noninvasive brain imaging techniques such as PET and NMR. Studies of neurotransmitter levels in spinal fluid and blood and other neurochemical indicators may prove helpful in the future. Clinical and laboratory evaluation may also reveal associated diseases such as strokes and Parkinson's disease. In more than 10 percent of cases with Alzheimer's disease, multiple brain infarcts are also observed. Dementia of the Alzheimer's type may occur in patients with Parkinson's disease more frequently than expected by chance. The presence of other neurological or psychiatric disorders does not exclude the diagnosis of Alzheimer's disease.

Other Methodological Issues in Assessing the Alzheimer's Disease Patient

A variety of methodological issues tend to be commonly overlooked in the development of criteria for the diagnosis of dementia and especially in the choice of assessment methods for identifying Alzheimer's disease. First, it is useful to recall that reliable group differences on a given measure--whether on CT scans, for example, or on psychometric tests--do not necessarily mean that the measure itself is useful when making decisions about the individual case.

Second, in validity studies, a number of complications surround the actual selection of subject groups. It is tempting, for example, to select patient groups that consist of clear-cut examples of the relevant conditions. On the other hand, however, the nature of clinical practice means that the test is most useful in making diagnostic decisions about cases that are more problematic. The validity of the test with this latter type of case may well be lower than it is for the more obvious members of one category or the other. The diagnosis of dementia, at least in the early stages, is never completely accurate. As a result, some cases used in diagnostic validation studies may not really be members of the class to which they are assumed to belong. In discriminating between dementia and depression, it is desirable to follow the subjects over time in order to confirm the diagnosis, since the long-term outcomes for the two conditions are very different.

The researchers must also take into account the problem of contamination in diagnostic studies, whereby a test becomes part of the criterion against which it is validated. For example, it often happens that a mental status test is used on a trial basis to help in the diagnosis, and the cases are later analyzed retrospectively to see if the test results relate to the diagnosis of dementia that was achieved. If the test contributed in any way to the decisionmaking process that was used to arrive at the diagnosis, it is not surprising that a later analysis reveals some validity.

A final methodological issue in formulating tests for differential diagnosis relates to the problem of where to set the cutoff point. Typically, test constructors set a cutoff point that achieves the maximum overall correct classification. However, this typically involves some incorrect classifications in both directions. When trying to discriminate between dementia and depression, the two types of error may not be considered equally undesirable. Since depression is a treatable condition, it may be a far more serious error to misdiagnose a depressed patient as demented than for the reverse to occur. It might be appropriate to set the diagnostic criteria to minimize this type of error even at the expense of a greater risk of falsely classifying an individual with Alzheimer's disease as depressed. Altering the cutoff point in this way typically results in a cutoff point different from that which achieves the minimum overall level of misclassification.

Measuring Cognitive Decline

One of the first goals in the assessment of patients suspected of having Alzheimer's disease is to measure the decline in intellectual functioning that occurred before the patient became ill. It is rare, however, to encounter patients for whom psychometric data are available from some previous time which is recent enough to be considered reliable, and not too close to the onset of the condition itself to be possibly contaminated by it. Direct measurement of decline by comparison of data obtained on two occasions is usually feasible only from the time the patient first comes in contact with the clinician. The initial assessment of the patient can then be compared with assessments made on later occasions to see if there is any further decline in functioning. This is sometimes useful when a diagnosis of Alzheimer's disease remains in doubt.

Any comparison of psychometric data obtained on two occasions involves technical complications. The test used must be very reliable. If not, a very large change in score must occur between the two testings in order to be outside the range of possible chance variation. In addition, an individual's score also changes from one testing to another because of such things as practice effects, regardless of any true change on the variable being measured. Ideally, appropriate test-retest data should be available for the test being used, making it possible to predict how the patient should perform on a second exposure to the test after a given interval. The patient's actual later performance can then be compared with this prediction.

Since the direct measurement of decline is difficult, there have been a number of attempts to devise indirect methods. These are inevitably based on the assumption that some aspects of intellectual functioning are more prone to decline as a result of disease than others. Those functions that are resistant to decline are then used to estimate the premorbid level, and those more susceptible to decline can indicate the present level of ability. A comparison between premorbid and present estimates can then be achieved. The earliest scales designed to measure intellectual decline were based on the assumption that vocabulary is resistant to decline, so scores on vocabulary tests were used to indicate premorbid levels. Unfortunately, these tests depend on assumptions that are only rough approximations of the truth. A number of studies have shown that vocabulary does not always remain unaffected by cerebral pathology, although it may be more resistant to decline than various other facets of cognitive functioning. The correlation between vocabulary scores and IQ is usually substantial but not so high as to avoid appreciable error in basing an estimate of IQ solely on vocabulary. Instruments using vocabulary in the measurement of intellectual decline are accordingly not accurate enough for use in the individual clinical case.

Another indirect way of measuring intellectual decline is the use of "deterioration indices" based on various combinations of subtest scores from the Wechsler intelligence scales. In addition to the assumption that the psychological consequences of dementia are the same as those of normal aging, the Wechsler and other deterioration indices involve presumptions similar to those relating vocabulary to the IQ. The deterioration indices are only rough approximations of intellectual deterioration.

The extent of intellectual decline has also been estimated by using the patient's educational and occupational level as a basis for judging what the IQ must have been. The main difficulty with this method is the considerable variation in IQ found in subjects with given educational or occupational records. This variation is not only large, it is greatest among those of lower occupational levels, who inevitably tend to be encountered more often in clinic practices.

It must be concluded that the instruments used to measure intellectual decline from premorbid levels are unsatisfactory. It is possible to test for further intellectual change after an initial assessment, but the absence of sound test-retest data relating to the various instruments should be kept in mind.

Tests of Memory Function

Decline in memory function is readily detected early in the course of dementia and, therefore, tests of verbal learning and/or memory at that stage are especially useful. Paired-associate learning tests and new-word learning tests may be helpful in discriminating between Alzheimer's disease patients and the elderly with functional disorders. Other instruments that may be used in the diagnosis of dementia are the various design-copying tests. These do not discriminate between organic and functional disorders as well as the verbal learning tests. A variety of other neuropsychological instruments, such as the Face-Hand test, can be of added assistance in the diagnosis of dementia.

Although early in the course of Alzheimer's disease reasonable levels of orientation may be preserved, an inability to give satisfactory answers to straightforward questions relating to orientation in space and time must raise suspicions of an ongoing organic process. Patients with Alzheimer's disease often perform poorly on tests of spatial perception and praxis. Language should also be assessed, as there is evidence of dysphasia in Alzheimer's disease patients with anomia, the most consistent type. These changes are rarely, if ever, seen as early as the decline in learning and memory. Finally, a variety of rating scales and questionnaires of mental status have been formulated specifically for use in elderly populations. These measures appear to serve quite effectively as initial screening devices.

Objective Laboratory Instruments

More useful information about brain activity in Alzheimer's disease may be obtained by multichannel computer-analyzed (quantitative) studies of EEGs, including assessment of sleep-wake cycles and response to stimuli. These studies of the EEG should be longitudinal and the results correlated with clinical signs, behavioral tests, and other laboratory studies.

A systematic, longitudinal study of evoked and cognitive potentials should be performed in patients with Alzheimer's disease. These studies should be repeated as the disorder evolves, and the findings must be correlated with clinical signs, neuropsychological tests, and other parameters. This information should provide a baseline that may be useful for staging the disease and for assessing therapeutic approaches.

Changes in the patterns of regional cerebral blood flow (CBF) should be correlated directly with detailed assessments of cognitive deficits and with other laboratory measures during the evolution of the disease. These approaches, in concert with the development of new markers of CBF, may be useful for monitoring the progression of disease and assessment of therapy.

In prolonged longitudinal studies, PET does offer the opportunity to correlate dynamic images with the clinical state, including neurophysiological testing, EEG, etc. Moreover, using C^{11}-labeled compounds, it may be possible to use retest paradigms. New approaches may be useful in delineating pre- and postsynaptic markers of a variety of transmitter systems, as has recently been achieved with PET images of the dopamine system. The efficacy of rCBF and PET in establishing various stages of the disease, documenting progression, and assessing the effects of treatment is unknown but worthy of investigation.

Rigorous quantitation of brain mass, cerebrospinal fluid (CSF) volume, and gray-white densities as determined by computerized tomography (CT) is needed. Relatively few CT studies have been directly correlated with clinical signs, neuropsychological tests, and other laboratory assessments. Such correlation may prove useful. Finally, the majority of CT studies have been cross-sectional, with one or two CT observations obtained early in the disease and with little long-term followup. Quantitative CT studies of Alzheimer's disease patients during the course of the disease are needed. It is important to correlate the evolution of CT images with results of autopsy findings.

Future Research Directions

The need to develop information on the sequence(s) of changes in Alzheimer's disease is critical. At the same time, there is a need to determine which tests are most useful in various stages of the disease. Work in diagnostic assessment in relation to dementia appears to have had its greatest success in the differential diagnosis of dementia, especially when distinguishing Alzheimer's disease from functional psychiatric disorders. Much effort has also been invested in finding ways to measure the decline in IQ from premorbid levels. The latter has proved difficult, and more study is necessary in order to devise a clinically satisfactory indirect means for the reliable measurement of cognitive decline.

Clearly, many problems involved in the assessment of the Alzheimer's disease patient still require resolution. When conventional forms of psychometric tests directed at the traditional problem of differential diagnosis are used, much greater attention needs to be given to the methodological issues noted above, especially in relationship to early diagnosis. Many of the most useful developments in the assessment of Alzheimer's disease may well come from the application of other techniques (e.g., rating scales, automated testing, and direct observation) to the problems of measuring change over time.

What is most urgently needed is a behavioral or biological marker unique for Alzheimer's disease. New technologies such as positron emission tomography (PET) and nuclear magnetic resonance (NMR) hold promise for the improvement of diagnostic accuracy. PET, for example, is providing new insights into the functioning of healthy and diseased brains and may eventually prove helpful in confirming the diagnosis of Alzheimer's disease, even in its early stages. Recent reports that PET can visualize dopamine receptors may presage the possibility of observing other neurotransmitter receptors in the living human brain.

EEG, evoked cortical potentials, and other analytic methods such as Brain Electrical Activity Monitoring (BEAM) may eventually also add valuable diagnostic information.

Although considerable controversy surrounds the ethics of doing brain biopsies--and certainly this issue needs careful and sensitive discussion--this may be a most useful diagnostic method, especially in a research setting.

Finally, it is essential that international standardized clinical criteria for the diagnosis of Alzheimer's disease be devised for use universally and in research. Instruments should be formulated that are linked to updated clinical criteria. In addition, these instruments should be validated against standardized, neuropathological criteria. Neuropathological criteria must be devised for the post mortem diagnosis of Alzheimer's disease, and age-stratified norms for normal and demented brain tissue in the older age ranges must be established.

Recommendations for the Development and Implementation of Research

These research recommendations are based on the identified knowledge gaps in diagnostic methodology, as specified above:

1. *Internationally standardized diagnostic research criteria,* operationalized, and integrated into DSM-IV and ICD-X should be developed, *based upon confirmation by standardized neuropathological criteria;* and linked to specifically developed Alzheimer's screening scales, and structured clinical interviews. This would include validation studies of the diagnosis of Alzheimer's disease, utilizing long-term outcome and autopsy studies to confirm or reject the initial diagnosis of Alzheimer's disease and to test those factors that are the most powerful predictors or correlates of a correct diagnosis of Alzheimer's disease.

2. *Markers for early detection:* Research is needed to develop and enhance psychometric, neurochemical, anatomic, electrophysiologic, metabolic, genetic, immunologic, and other *biomedical/behavioral techniques, for early detection of Alzheimer's disease.*

3. *Longitudinal studies* of Alzheimer's disease with confirmatory autopsy are needed in order to accurately delineate the evolution of neurological and psychological signs. Reliable *approaches for estimating the decline of cognitive function* from premorbid levels require further research, as do approaches to sensitively assessing changes in intellect, language, and social function over the course and stages of disorder.

4. In cases where *serious discrepancies* exist *between degree of cognitive deficit and extent of brain impairment,* painstaking systematic investigations should be undertaken. Patient studies of brain metabolism using PET, CT, CBF, EEG, EP, and psychological techniques could make a significant contribution to gaining a better understanding of these correlations at the various stages of progression of Alzheimer's disease.

These research objectives would be aided by periodic state-of-the-art conferences on these identified problem areas; research planning workshops to identify specific emerging scientific opportunities; earmarking additional resources for research in diagnosis; and training additional investigators whose capabilities would encompass the relevant disciplines of geriatric medicine, neurology, psychiatry, psychology, neuropathology, epidemiology, genetics, and neuroradiology.

Requests for applications (RFAs) with specific goals, program proposals, and training grant proposals are all needed to develop the necessary research and research capabilities in these areas.

Finally, a national multicenter diagnostic validation study, utilizing medical centers with established clinical research programs in Alzheimer's disease, should be supported.

Chapter 4

Research on Clinical Course

Current Knowledge Base

Present knowledge concerning the clinical course of Alzheimer's disease is quite limited. Since early accurate diagnosis is difficult, there is relatively little information on the natural history of the disease in its early phases. Typically a patient is brought to the attention of the physician only in the later stages of the illness and in settings other than research medical centers.

Knowledge about the course of Alzheimer's disease currently comes primarily from observations of clinicians and, to a lesser extent, from prospective clinical investigations. Reisberg et al. (1982) describe the clinical course and changes in performance on psychometric tests of patients with Alzheimer's disease. They find that initially patients complain of forgetting where they placed familiar objects and forgetting names they formerly knew well. While no objective evidence of memory impairment is apparent in the clinical interview or in social and employment situations, some psychometric indices may be found to be below average. It is extremely difficult to determine whether this represents the first stage in a progressive dementing illness or whether these symptoms represent only the manifestation of the stable "benign senescent forgetfulness" state described by Kral decades ago.

Following this, clinical deficits do appear; the individual may demonstrate decreased facility in remembering names of people who have just been introduced or may retain very little from reading a passage in a newspaper. Such persons may have no recall at all of some recent events and yet recall others well. In contrast to these lapses which occur occasionally in most people with normal mental functioning, the person with Alzheimer's disease is unable to recognize or recall even the context or related circumstances of the forgotten item or event. These difficulties become evident to intimates, and decreased performance is manifested in demanding situations at work. The patient may become seriously lost when traveling to an unfamiliar location. These symptoms are commonly accompanied by mild to moderate anxiety and by performance on psychometric tests well below average.

Nevertheless, the Alzheimer's disease patient may still obtain a perfect score on the 10–item Mental Status Questionnaire.

This preliminary stage of impairment is typically followed by more serious decline. Concentration deficits can usually be elicited, and patients also display decreased knowledge of recent events, both in the context of their own personal lives and in the context of the world around them. Though patients generally have no problem traveling to familiar locations, ability to travel alone is notably curtailed, and difficulties with managing personal finances may become apparent. Complex tasks can no longer be performed accurately and efficiently. Denial is often the dominant defense mechanism at this stage, together with symptoms such as social withdrawal, flattening of affect, and loss of initiative, tact, and judgment. By this juncture, patients typically make 3 to 9 errors on the Mental Status Questionnaire; yet they may be able to function safely in a limited familiar environment with familiar routines.

In the next phase, patients can no longer survive without some assistance. They are unable, in clinical interview, to remember relevant facts regarding their own address, or phone number, or the names of close family members or of their high school or college, though they invariably know their own names and those of their spouse and children. Toileting and eating activities remain intact, though difficulty in selecting the proper clothing to wear is a common problem. Even in this phase, there may be episodes of lucidity.

As the disease progresses, patients may occasionally forget the name of their spouse and become largely unaware of all recent events and experiences in their lives. Typically, they are by now unaware of their surroundings, the year, or the season. Diurnal rhythm frequently becomes disturbed, and episodes of incontinence may appear. Personality and emotional changes often manifest themselves and are quite variable, often including delusional and paranoid behavior, such as accusing a spouse of being an imposter, or talking to imaginary figures in the environment; obsessive symptoms, such as repetitive washing of the dishes; anxiety symptoms, agitation, and newly manifested violent and abusive behavior; and an inability to act because of the inability to retain a thought long enough to pursue a purposeful course of action. The changes just described—particularly the inability to recognize a spouse or other caregiver, incontinence, and/or emotional outbursts—are especially difficult burdens for the caring family members and are often the reasons for seeking institutional care for the patient.

Ultimately, all verbal abilities are lost; the patient is incontinent of urine, requires assistance in toileting and eating, and may lose the ability to walk. At late stages of the disease, generalized cortical, as well as focal neurologic, signs and symptoms are frequently present. Invariably, patients with late dementia make 10 errors on the Mental Status Questionnaire.

Future Research Directions

Although the above observations are exceedingly rich clinically and provide a useful starting point for further research, nevertheless many important issues relating to clinical course remain unexamined. There is a general consensus about the latest phases of Alzheimer's disease, and there is a reasonable degree of agreement about the approximate sequence of intermediate deficits. However, there is still great difficulty recognizing the disease in the early stages. Little attention has been paid in the research literature to the enormous variability in rate of deterioration and the vast differences in duration of disease—from 2 to 20 years. Investigators have often failed to control for confounding factors such as years of education, general physical health, premorbid personality features, family and informal supports, and capacity for self-care. Few longitudinal studies of the course of illness have been carried out, family history is commonly not included in research designs, and individual differences are often overlooked.

Typically, performance on diagnostic screening instruments and psychometric tests has not been especially well correlated with actual capacity for self-care and for life in the community. What intervening factors might be responsible for shaping, hastening, or delaying the inevitable progression of symptomatology? What are the roles of premorbid character style, family support, structured living arrangements, etc., on the rate of disease progression, severity of illness, the development of secondary psychiatric symptoms, and longevity/mortality?

Can behavioral and/or biological markers be developed which can reliably distinguish instances of "benign senescent forgetfulness" from prognoses of a more ominous course? Do particular symptom clusters appear earlier and more prominently in familial Alzheimer's disease? How similar is the clinical course of illness in Alzheimer's disease and multi-infarct dementia? While the latter illness is commonly associated with a spottier course, with stepwise progression, and with focal neurologic signs, these clinical observations have not been uniformly confirmed at autopsy. Similarly, what accounts for those discrepant cases in which the course of behavioral and cognitive deterioration is steep and unremitting, yet the histopathological evidence is negative for Alzheimer's disease (and vice versa)? Is the variable manifestation of secondary psychiatric symptoms (such as paranoia, obsessional behavior, depression, anxiety, and hallucinations) during the course of illness linked more specifically with exacerbated, localized neural damage or with specific, secondary neurochemical imbalances? Can measures be developed that will accurately predict when a given symptom will occur in a given patient, beyond assuming that cognitive deterioration will progress? While certain core symptoms such as difficulty with new learning; disorientation for time, place, and person; apraxia; and ultimately, aphasia are often cited as hallmarks of Alzheimer's dementia, secondary psychiatric symptoms are far less predictable in nature and often pose far greater burdens for the caregiver.

Finally, in terms of systematic longitudinal research, which tests are most useful for sensitively monitoring the increasing rates and severity of deterioration in Alzheimer's disease? Hersch's Extended Scale for Dementia and Reisberg's Global Deterioration Scale for Assessment of Primary Degenerative Dementia appear to be useful measures in documenting the progressive global decline in cognition, behavior, and affect in Alzheimer's disease patients. However, the development of more sensitive and specific biological and behavioral measures is urgently needed.

Recommendations for the Development and Implementation of Research

1. Large-scale, prospective, longitudinal multidisciplinary epidemiologic studies are needed in order to better understand the full and varied course of Alzheimer's disease. Such studies should include a variety of objective measures of cognition, language, brain structure and function (including neurochemistry and histopathology), measures of metabolic, endocrine, and immunological functions, and measures of genetic and environmental influences, behavioral symptoms, functional abilities, and needs, etc.—all with confirmation of diagnosis by autopsy. The development of sensitive and specific psychometric, behavioral, affective, physiological, and neurochemical longitudinal assessment instruments, capable of reliably measuring change at multiple points in time, is essential.

2. Such studies could take place within the context of an international program of clinical research on the course and outcome of Alzheimer's disease in diverse populations, with special emphasis on behavioral and/or biological factors that hasten or delay the progression of symptomatology and that influence the level and nature of associated psychiatric symptomatology.

3. Such studies should examine variations in the clinical course of Alzheimer's disease, with particular attention to possible risk factors or other cultural and/or environmental differences. Moreover, they should take into account the impact of individual differences and variability in severity and duration of illness, rate of deterioration, and capacity for self-care.

These studies should be undertaken through the collaborative efforts of the appropriate Federal agencies, via the vehicle of targeted requests for applications (RFAs), contracts, and program proposals. Investigator-initiated grant proposals should continue to be the most important base for national research on the course of illness in Alzheimer's disease.

Chapter 5

Research on Treatment

Current Knowledge Base and Future Research Directions

Pharmacologic Interventions for the Treatment of Cognitive Impairment

Cholinergic Agents

Over the past decade, knowledge regarding the complex process involved in brain function has advanced tremendously. Particularly important in this respect is the compelling evidence accumulated from a number of lines of research suggesting that Alzheimer's disease is associated with the impaired function of neurons that utilize the chemical messenger acetylcholine in the cerebral cortex. Scientists have demonstrated that drugs that interfere with the action of acetylcholine in the brain can produce cognitive impairments in the young that resemble those seen in Alzheimer's disease. Scopolamine, for example, which antagonizes the neurotransmitter acetylcholine, has been found to specifically impair the encoding, consolidation, and retrieval of memories. On the other hand, drugs that enhance acetylcholine activity (e.g., lecithin and anticholinesterase) appear to produce some small improvement in memory in some Alzheimer's disease patients and more significant improvements in experimental animals.

The convincing evidence that central cholinergic function is diminished in Alzheimer's disease has led to three major pharmacologic treatment strategies:

- Attempts to enhance the synthesis and release of acetylcholine by increasing precursor levels
- Attempts to enhance cholinergic activity by intervention in the synapse or at the receptor site
- Attempts to enhance cholinergic activity by combining precursor therapy with compounds that enhance cerebral metabolism

The first strategy has led to more than 20 clinical trials with either choline or lecithin in Alzheimer's disease patients. Although these studies appear to suggest that precursor therapy is not an effective treatment in Alzheimer's disease, it is possible that such treatment may not have been adequately tested, since most of the patients tested were in late stages of the disease.

The second strategy has led to trials with the acetylcholinesterase inhibitors physostigmine and tetrahydroaminoacridine (THA) and with the muscarinic agonist arecoline. Physostigmine has been shown to produce a modest facilitation of learning and memory in both Alzheimer's disease and normal subjects when administered by intravenous infusion, but the magnitude and duration of the change, safety considerations, and the logistical problems in administration greatly diminish the practical significance of this finding. More recently, trials with oral physostigmine have been undertaken, and early results are encouraging. The muscarinic agonist arecoline has also been evaluated in several studies and was shown to produce a modest facilitation of learning and memory performance in both normals and patients diagnosed with Alzheimer's disease.

The third strategy for cholinergic intervention has led to trials in which lecithin was combined with the much studied "nootropic" compound piracetam. In an open trial, the combination treatment was found more effective than treatment with either component in facilitating learning and memory-task performance in both aged rats and some Alzheimer's disease patients.

Finally, limited evidence has recently been presented for the argument that any effects of choline or lecithin are due to generalized cell membrane effects rather than specific cholinergic effects. Some attention has been focused on a new Israeli compound known as active lipid that is reputed to enhance membrane permeability more effectively than either choline or lecithin. The compound has apparently not yet been evaluated in a controlled trial in Alzheimer's disease.

Neuropeptides

Among the neuropeptides evaluated in Alzheimer's disease, the greatest interest has been attracted by fragments and analogs of ACTH and analogs of vasopressin. Included are ACTH 4–10, an ACTH 4–9 analog, lysine vasopressin, desglycinamide lysine vasopressin, desglycinamide arginine vasopressin, and 1–desamino–8–d–arginine vasopressin. Clinical trials of these compounds in Alzheimer's disease have been disappointing. While positive findings have been reported in some isolated patients, the magnitude of any drug effects on learning and memory in Alzheimer's disease has been, at best, quite modest.

Vasodilators

Compounds currently on the market and used by some practitioners to treat both Alzheimer's disease and multi-infarct dementia include paraverine, isoxsuprine, and cyclandelate. The efficacy of these compounds has not been established, and the Food and Drug Administration (FDA) has moved to challenge their use in Alzheimer's disease. Among the compounds under investigation, the vasodilator nylidrin has been studied in multicenter trials and awaits a final FDA decision on marketing. The drug appears to exert modest effects on behavior or mood but has not been shown to directly affect learning and memory in patients with Alzheimer's disease. Several vasodilators are currently being evaluated in multi-infarct dementia, but greatest interest has focused on calcium channel blockers such as nifedipine and nimodipine.

Metabolic Enhancers

The most widely studied and used of the so-called cerebral metabolic enhancers is dihydroergotoxine. This drug has a broad range of metabolic effects and appears to be of some utility in the management of certain select Alzheimer's disease patients. It has not, however, been shown to directly affect learning or memory.

Among the other compounds in this relatively nonspecific class of drugs that have recently been studied in relation to Alzheimer's disease are naftidrofuryl, pentoxifylline, and piracetam, together with its many analogs. The effects of these drugs reported thus far have not been dramatic in patients diagnosed with Alzheimer's disease.

Other Compounds

Among the other drugs recently studied or currently under investigation in Alzheimer's disease are naloxone, an opiate antagonist, and its oral analog naltrexone; alaproclate, a specific inhibitor of 5-HT reuptake; CGS7135A, a selective alpha-2 receptor blocker; centrophenoxine, a compound that reduces the age-related accumulation of lipofuscin; and several chelating agents, based on the tenuous hypothesis that brain aluminum accumulation is of etiologic significance in Alzheimer's disease.

At present, no clinically effective pharmacologic treatments are available for the cognitive symptoms that comprise the hallmark of Alzheimer's disease. A great deal of research is underway, however, and some potentially important findings are emerging.

Pharmacologic Interventions for the Treatment of Secondary Psychiatric Symptoms in Alzheimer's Disease

Family members and caretakers of the Alzheimer's disease patient often note that the secondary symptoms of dementia are more difficult and taxing to manage and deal with than the core symptoms per se, namely, intellectual deterioration and disorientation. The most common secondary psychiatric disorders include depression, anxiety, paranoia, and obsessionalism, all of which may be associated with symptoms of impaired sleep, withdrawal, wandering, and delusions. These symptoms are often seen to exacerbate the severity of illness, contributing to excess disability for the patient, excess burden on the resources of the family, and higher rates of institutionalization.

While psychotropic medications are commonly prescribed for patients with Alzheimer's disease, and general reviews of psychopharmacology in the elderly have argued that antipsychotics, anxiolytics, and antidepressants are more useful than any of the medications mentioned above, surprisingly few empirical studies have systematically examined the relationship of neuroleptic blood levels to clinical response in Alzheimer's disease. Some of the most common categories of medication used for treatment of secondary psychiatric symptoms are discussed below.

Drugs for Psychosis and Agitation

Basic information about relationships between blood levels and clinical outcome and/or side effects of neuroleptics is currently unavailable, despite the frequency with which such agents are used in Alzheimer's disease patients, particularly in institutionalized settings, and despite evidence that a major side effect of neuroleptic use in the elderly, tardive dyskinesia, may be related to blood levels. Optimal blood levels of lithium carbonate, a drug with effects on emotional lability and aggression, have not been systematically determined for the older patient diagnosed with Alzheimer's disease. Finally, and perhaps most important, it has been suggested that anticholinergic agents, which are commonly given with antipsychotic medications, often cause impaired memory and confusion, yet no controlled studies on the relationship between blood levels, clinical impact, and side effects have been carried out in Alzheimer's disease.

Antidepressants

Generally, when tricyclic antidepressants are administered to the elderly, clinical effects are less predictable than in younger patients, and this is especially true when dementing illnesses coexist. Because mood disorders frequently appear concomitantly with Alzheimer's disease, several current studies are focusing on the treatment of depression in the face of chronic, progressive, dementing brain disease. One investigator now studying patients with Alzheimer's disease of late onset, both with and without depression, is attempting to determine if these individuals differ with respect to antecedents and response to treatment with antidepressants. Do the two groups have different outcomes regarding cognitive function? Another scientist is evaluating tricyclic treatment of mood disorder in Alzheimer's disease patients in an effort to understand better the course and outcome of pseudodementing and true dementing states, especially when the latter appear concomitantly with mood disorders.

The fact that there is an age-related increase of monoamine oxidase (MAO) in the brain of elderly individuals has led some clinicians to consider the use of MAO-inhibitors in old age. Although some clinical reports argue that this is a safe practice, the package inserts on MAO-inhibitors available in the United States list chronological age as a relative contraindication (due to the drugs' vascular effects). While some have used MAO-inhibitors to treat the affective disorder that is such a common concomitant of Alzheimer's disease, to date no controlled trials of this medication have been reported in the literature.

The Impact of Psychotropic Medication on Memory Function in the Face of Progressive Dementing Behavior

Little detailed information is available regarding side effects and the short- and long-term cognitive effects of psychotropic agents in the elderly, particularly in Alzheimer's disease patients. On the basis of clinical impression, some have suggested that antidepressants and psychostimulants are as effective in improving the nonspecific aspects of cognition (e.g., attention and motivation) as any of the so-called specific cognitively acting agents (e.g., the ergot alkaloids). On the other hand, questions remain as to how these drugs interact with and enhance the effects of psychotherapy. While it is plausible that such agents could facilitate psychotherapy if attention or memory were improved, it is equally possible that such agents could impede psychological treatment because of state-dependent or decremental effects on memory. As Alzheimer's disease is associated with major deficits in the cholinergic system, more systematic data are needed regarding the impact of antidepressant medications, even those with less significant anticholinergic effects.

Sleeping Medications and the Alzheimer's Disease Patient

A major nonspecific pharmacologic problem relating to Alzheimer's disease patients, especially those who are institutionalized, is the rational use of sleeping medications. Recent studies suggest that noctural sleep is severely disrupted in Alzheimer's disease patients and that the periods of sleep that are most refreshing (i.e., stages 3 and 4) almost completely disappear in the severe stages of Alzheimer's disease. Partially in an effort to control the noctural wandering that appears to be associated with broken and impaired sleep in dementia, many institutions widely prescribe soporifics for their Alzheimer's disease patients.

At present, the 15 percent of the population that is over 60 years of age consumes 33 percent of all prescriptions for secobarbitol and diazepam. Such compounds can impair daytime functioning by directly affecting daytime alertness and secondarily by inducing sleep in the daytime, further impairing the ability to sleep the following night. Several such compounds have long metabolic half-lives and accumulate to levels well above the peak of a single dose. For example, an active metabolite of the most commonly prescribed hypnotic, flurazepam, has a half life of over 70 hours in the elderly. These considerations should lead to a more careful evaluation of the safety of such drugs as well as a more systematic evaluation of nonpharmacologic interventions for elderly patients with Alzheimer's disease who use drugs to sleep.

Psychosocial Interventions and Management Techniques in Alzheimer's Disease

Psychological Interventions for Elderly with Complaints About Memory and Mild Cognitive Impairment

Studies to improve attention. The quality of attention has been found to decline with advancing age, including the ability to selectively attend to stimuli, to maintain attention to a particular task, and to resist fatigue in the face of repetitive tasks. These difficulties are exacerbated as cognitive impairment progresses.

Some investigators, having noted that high levels of anxiety impair attention, have attempted to determine whether relaxation techniques might reduce anxiety and improve attention. Anxiety reduction techniques, such as deep muscle relaxation, however, have been shown to have only minimal and perhaps nonspecific effects in the elderly with cognitive impairment.

The effect of training on motivation and arousal must be considered in evaluating techniques such as relaxation training. Since the Yerkes-Dodson law was first proposed (1908), it has been argued that the relationship between motivation and performance is curvilinear, i.e., increases in motivation or arousal have a beneficial effect on performance when motivation is initially relatively low, but tend to disrupt performance when motivation is initially strong. Many studies have found evidence for this inverted-u relationship between motivation and performance. Thus, it may be that studies of attempts to modulate anxiety, motivation, and arousal will have to consider the cognitively impaired individual's initial levels of such factors, considered in conjunction with the progressive rate of cognitive decline.

Studies of organizational techniques. Several studies of psychological treatments in elderly patients with mild cognitive decline have shown positive effects from organizational techniques, i.e., mnemonics. Improvement in affect, ability to do practical memory tasks, and list learning in patients receiving group mnemonic training has been reported.

These interventions often involve the use of mnemonic devices based on visual image associations. A typical technique is the loci method, in which the individual first names several locations in a familiar building or setting, such as his or her home. Once these locations have been learned to a criterion score, the individual forms a visual image association between the first item of a list to be remembered and the first location in the house. Each subsequent item to be remembered is then associated with the next location in the house. To recall the list, the individual takes a mental "walk" around the house, "stopping" at each location to retrieve the visual image associated with it that serves as a retrieval cue for the item to be remembered. This mnemonic not only has an impact on the recall of lists, but it also helps individuals retain the original ordering of the lists.

A potential problem with the use of such mnemonics is that the elderly appear to have difficulty generating and remembering visual image associations. Craik's levels-of-processing framework would suggest that this difficulty arises because the elderly do not sufficiently process the material to be learned at encoding. Despite this difficulty in forming image associations, positive effects similar to those seen with the loci mnemonic have been noted for paired-associate learning using visual imagery in normal elderly individuals. In addition, recent work has indicated that the elderly can benefit from instruction that leads to more elaborate processing at encoding. An example is the finding that recognition memory for faces can be improved in the elderly, as in younger subjects, if they are asked to judge a person's pleasantness while trying to encode that person's face. Neither of these strategies has been tried with individuals having more than mild cognitive impairment.

Although some positive effects have been seen in several studies of subjects with mild cognitive loss, most of these innovative techniques, based on current theories of information processing, have not been applied to elderly individuals with more serious levels of progressive cognitive impairment. For the most part, behavioral studies with Alzheimer's disease patients have utilized far less sophisticated experimental approaches.

Psychological Interventions for Elderly Patients with Moderate to Severe Levels of Cognitive Impairment

Reality orientation. For at least 20 years, scientists have been studying psychologic intervention to improve and/or ameliorate cognitive deficits in individuals with senile dementia. Probably the most commonly studied intervention has been "reality orientation," an approach which attempts, primarily by repetition and reinforcement of correct responses, to reorient demented nursing home residents. Although some studies have shown positive results, more carefully controlled investigations have found that gains decrease rapidly after the reality orientation classes are discontinued. Moreover, positive responses may result from nonspecific factors such as the increased attention given to class members. In addition, reality orientation did not provide a measurable improvement in behavior even in subjects who showed reorientation. In general, these studies suffer from lack of control of medications, small numbers of subjects, use of nonblind raters, and failure to use widely accepted psychometric measures to precisely identify diagnosis and degree of impairment.

Image association techniques. Few controlled studies evaluating the use of image association techniques to improve memory have been published. Although one study indicated that image association techniques were beneficial to brain-injured patients attempting to learn paired associates or to perform a face-name task, the researcher did not control for nonspecific aspects of treatment nor for spontaneous remission. Further work in this promising area is indicated.

Combined pharmacologic and psychologic interventions. Very little attention has been paid to the combination of pharmacologic and psychologic interventions in the treatment of Alzheimer's disease. One study has combined medication with either supportive psychotherapy or cognitive training for list recall using the method of loci in an attempt to enhance the efficacy of dihydroergotoxine (Hydergine). Subjects receiving pharmacotherapy plus cognitive training improved more on a psychometric test of memory and list learning than subjects receiving the drug plus supportive psychotherapy. No differences were seen between groups, however, on behavioral measures. The fact that cognitive training could not augment even the modest behavioral effect of the drug may argue against its potential as a practical intervention. On the other hand, improvement of function was seen on the task in which the subjects were trained, and it may be unreasonable to expect cognitive training in list learning to generalize to overall behavioral development without specific efforts to relate the training to the activities of daily living.

Summary of psychological interventions for intellectual decline. Although some evidence for clinical effects of cognitive retraining in the elderly demented has been found, outcome studies of such therapies have suffered from lack of controls as well as the lack of sophistication of the interventions proposed. The basic method used in the reality orientation studies is typically repetition, which appears to improve short-term but not long-term memory. To date no studies have been published in which Alzheimer's disease patients have used the sophisticated techniques commonly used with less impaired elders, and minimal attention has been paid to the important impact of individual differences among elderly subjects with memory deficits.

Another major gap in these psychological studies has been the concentration on cognitive improvement, with maximal neglect of the secondary psychiatric symptoms that so often color the clinical picture in Alzheimer's disease. Hysterical reactions, depression, anxiety attacks, and obsessional behavior are all targets of individual psychotherapy in young and old alike, yet little discussion has been given to using psychotherapeutic techniques to aid the Alzheimer's disease patient suffering from these problems. Verwoerdt has argued that psychotherapy with patients diagnosed with Alzheimer's disease must be considered an essential part of a comprehensive treatment approach. Yesavage and Karasu have argued that refusal to even consider the option of prescribing individual psychotherapy to Alzheimer's disease patients is often due to a "gerontophobic" reaction on the part of the physician. A great need exists for systematic exploration of the role of individual psychotherapy as an adjunct to treatment of the demented patient.

The roles of affect and motivation in retraining efforts are also poorly understood. It has been well documented that memory complaints are often better correlated with depression than with the actual degree of cognitive impairment. A mood-specific memory effect has also been documented in nondemented individuals. This finding suggests that material learned when one is happy is better recalled when happy, and material learned when one is sad is better recalled in that mood state. The effects on cognitive performance of interventions aimed at improving motivation, self-image, and affect remain to be explored in samples of Alzheimer's disease patients.

In addition, few published studies to date have attempted to combine promising therapies. For example, it would make sense to give preliminary training in techniques such as relaxation to improve concentration or training in visual imagery ability prior to teaching complex mnemonic devices that are based on visual imagery. Thus there are many areas in which knowledge of the outcome of cognitive retraining in the cognitively impaired elderly is lacking.

Finally, little research has been done on the effects of medications on cognitive training. Medications that have psychostimulant effects might be expected to enhance learning and might make it easier for Alzheimer's disease patients to assimilate new techniques. On the other hand, common psychotropic agents have been shown to have state-dependent effects on learning, which possibly could lead to learning impairment, given certain changes in medication type and dosage. Other compounds with anticholinergic effects that are commonly used with the elderly can also be expected to impair function in the Alzheimer's disease patient.

In summary, while many sophisticated programs are available for use with the mildly impaired, controlled studies with the severely demented are lacking. Future research in this area should attempt to develop new approaches based on the nature of the cognitive and affective disorder unique to Alzheimer's disease and to explore further the combined use of medication with psychological approaches.

Behavioral Interventions for Alzheimer's Disease Patients with Specific Behavioral Problems

Behavior modification has been used successfully to change a wide variety of problem behaviors associated with demented institutionalized elderly including agitation, self-injurious behavior, screaming, urinary incontinence, and insomnia. There are, however, several cautions and limitations to these approaches. Most importantly, these programs do not work in isolation, and they are only relatively effective when carried out in the context of caring individual relationships with therapists, careful medical assessment, a supportive and physically adequate environment, and a familiar fixed daily routine. Such interventions cannot compensate for isolation, medical mismanagement, and decrepit physical facilities. Second, the term "behavior modification" is highly emotionally charged and often tends to lead to rejection of a program on "humanitarian" grounds. Finally, it is necessary to train caretakers, either professionals or families, in how to effectively and empathetically use behavioral techniques. It is unrealistic to expect an expert, behaviorally trained psychologist to be available to develop, initiate, and maintain individualized programs for large numbers of patients. It is far more useful and cost effective to develop ways of teaching these techniques to groups of caretakers and to staff.

Treatment and the Family

The role of the family in the treatment and support of the patient with Alzheimer's disease has recently attracted considerable attention in the research community. It is becoming increasingly obvious that Alzheimer's disease in a family member can have a devastating economic and emotional impact on family members and relatives caring for the dementing individual. Ongoing studies are exploring clinical relationships between family systems and dementia: a) evaluating how social role function, physical and mental health, and subjectively experienced strain over time, mediate the impact of the disease on caregivers and on patient alike; b) evaluating the differential efficacy of family and group counseling for caregivers as a means of reducing the burden of care and of making home placement feasible for families who desire it; c) assessing the extent of emotional and economic burden on the caregiver, in a random, stratified sample of the population; and d) studying the impact of support groups for caregivers to determine their effects on levels of depression, anxiety, and feelings of burden in family members.

Preliminary results from these studies suggest that caretakers of Alzheimer's disease patients often sustain severe and chronic levels of stress, often manifesting "burn-out," exhaustion, and the development of iatrogenic disorders. In addition, family members often lose their leisure time, social life, friends, and income. More effective psychological and social methods of family support are clearly needed in order to maintain the family equilibrium and to treat the specific psychiatric disorders that arise from the stress of caring for an elderly relative with Alzheimer's disease.

Numerous questions remain, including which type of interventions are most effective with which types of caregivers, for what nature of behavioral problems? What behaviors, or combinations of circumstances, are most powerfully associated with the development of morbidity in the caretaker, and which with the ultimate decision on the part of the caretaker to institutionalize the patient? Which psychotherapeutic interventions or types of family or community support best assist the caretaker to survive psychologically and to understand better his/her own emotional reactions of guilt, anger, and grief and which best help to maintain the patient in the context of the family for as long as possible? These issues stand in need of compassionate scholarship.

Psychosocial (Environmental) Aspects of Treatment

A major effort in the psychosocial treatment of Alzheimer's disease is aimed at keeping the patient at home with family and in the community as long as possible. The rationale for delaying institutionalization has been reviewed by Kahn and Tobin (1981) who argue that "overdosing" elders with social assistance may lead to elevated mortality and morbidity, especially since such efforts often lead to institutionalization. The few controlled studies that exist show that day-care or day-hospital programs can effectively reduce the need for inpatient care. Kahn and Tobin identify several aspects of community mental health treatment of demented elderly that they feel essential to good outcome: a) early intervention before the family is completely burnt-out and will have nothing more to do with the patient, b) minimum intervention with hospitalization only as a last resort, and c) guarantees that needed services will not vanish once the patient is established in community care services. Virtually no controlled studies exist of these and other factors that would enter into a successful community-based program in the United States. Model programs could be initiated that would provide controlled data regarding those factors that lead to the most productive program.

Despite the goal of community care, institutionalization eventually does become necessary for many patients with severe deficits. Although the role of the institutional environment in the treatment of the Alzheimer's disease patient has been minimally explored, preliminary evidence suggests that, compared to general psychiatry wards, wards housing Alzheimer's disease patients tend to have reduced privacy, few opportunities for activities, and little freedom of movement.

A study by Lawton suggests that environmental changes may have substantial effects on the manifest behavior of demented patients. Other clinical papers suggest that reorganizing wards along the lines of "token economies" may be effective, although here, too, no controlled studies have yet been carried out.

Little is known regarding the range of behavioral plasticity that might still be available to the Alzheimer's disease patient, at different stages of illness, in response to environmental manipulations. It is important to determine whether the increasing perceptual difficulties, the growing problems in understanding and interpreting language and print, and the progressive loss of orientation in time and space can be somewhat compensated for by the appropriate structure and constellation of environmental stimuli. Difficulties in locating the bathroom, negotiating the stairs, using hot water in the bath, etc., could possibly be ameliorated by appropriate architectural, mechanical, or other safety supports in conjunction with behavioral management techniques. Multidisciplinary research in this area is called for. Studies of the impact of noise, activity, exercise, sensory deprivation, timetables, and social organization on the Alzheimer's disease patient could also help the clinician provide his patient with the appropriate care to ensure optimal homeostasis.

Research Recommendations and Mechanisms for Implementation

Basic Research and the Study of Neurochemical Deficits

Investigators should continue to explore the cholinergic hypothesis in the development of new treatment agents for the primary cognitive impairment in Alzheimer's disease. Other neurochemical deficits that have now been linked with Alzheimer's disease, such as changes in the noradrenergic and serotonergic systems, should also be evaluated in the search for effective treatment agents.

Studies are urgently needed to evaluate the indications for, and efficacy of, psychopharmacologic agents in the treatment of secondary psychiatric symptoms and syndromes occurring concomitantly with Alzheimer's disease. The most common secondary disorders include depression, anxiety, paranoia, and obsessionalism, which may be associated with symptoms of sleep disturbance, withdrawal, wandering, and delusions. While some reports suggest that neuroleptics may limit and control symptoms quite well, other findings suggest that such agents exacerbate confusion, disorientation, and sleepiness in dementing patients. Accordingly, the relation of blood levels of commonly prescribed psychotropics (e.g., major and minor tranquilizers, antidepressants, anxiolytics, and hypnotics) to clinical effects on mood and cognition and to side effects requires careful, systematic research.

Animal Models and Alzheimer's Disease Correlates

The identification of naturally occurring animal diseases and the development of new experimental animal models, based on actual neuropathological findings in human populations, should be strongly encouraged. Although the induction of anoxia in rats or the use of electroconvulsive therapy-induced amnesia may mimic the effects of advancing chronological age, such techniques lack specific correlates with the neuropathology of Alzheimer's disease. Experimental procedures, such as the lesioning of the nucleus basalis in laboratory animals, may lead to closer approximations of the disease state in man.

The Measurement of Cognitive Change in Drug Outcome Studies

The development of new and more specific psychometric models that can more accurately distinguish among memory, motivation, and attention effects over time will contribute significantly to the precision of treatment outcome research.

Other Methodological Issues in Assessing the Alzheimer's Disease Patient

Though few have been undertaken, studies of the efficacy and impact of psychotherapy--especially in the early and middle stages of Alzheimer's disease--should be seriously considered. Studies of classical, individual psychotherapy techniques for the treatment of depression, anxiety, and phobic behavior secondary to dementia also deserve careful attention; and clinical trials assessing the concomitant effectiveness of drugs and psychotherapy should be systematically undertaken in this population.

The development of humane and innovative behavioral interventions for the modification of problem behaviors in Alzheimer's disease patients requires intensive research attention. Improved approaches for shaping appropriate eating behaviors, modifying chronic screaming, controlling incontinence, limiting combativeness, preventing wandering, etc., would contribute significantly to lightening the burden of care. Carefully controlled studies of behavioral interventions have been few in number, with minimal attention to the generalizability of treatment effects or to the maintenance of behavioral gains, even over the brief periods of time.

Influence of the Environment on Dementia

Research is needed to evaluate the impact of the environment itself on shaping and maintaining positive behaviors in the individual with Alzheimer's disease. More information is needed regarding the range of behavioral plasticity in Alzheimer's disease, and the optimal manner in which time, space, and level of stimulation are best organized, in order to assist the patient in achieving the most autonomous adjustment in the home, as well as in institutional settings. The integration and guarantee of available services to the family sustaining an Alzheimer's disease patient in the community must also be considered an integral part of any rational treatment plan.

Efficacy of Support and Self-Help Groups

The family, as well as the patient, is a victim of this dread disorder. Caretakers of Alzheimer's disease patients sustain severe and chronic levels of stress, often manifesting "burn-out," exhaustion, and associated iatrogenic disorders. Studies are needed to examine the impact of using support and self-help groups to ameliorate stress in caregivers and to evaluate the most effective ways in which to organize such groups.

Management and Coping Skills

Studies are needed to determine the efficacy of and best approaches to teaching behavioral management strategies and coping skills to caregivers.

Behavior Intolerable to the Caretaker

Studies are needed to establish the utility and specificity of intensive individual and group psychotherapy for those caregivers at greatest risk for the development of psychiatric disorder and to evaluate which patient behaviors are significantly associated with the family's decision to institutionalize.

Chapter 6

Research on the Family

Current Knowledge Base

Dr. Lewis Thomas of Sloan-Kettering recently observed that "Alzheimer's causes more damage to the family than any other disease I can think of" (*New York Times Magazine*, January 16, 1983). Indeed, both empirical studies and anecdotal accounts underscore the pivotal role of the family in the short- and long-term care of the patient with dementia. Perhaps as many as one million older persons with Alzheimer's disease are currently being cared for in the community by their families.

The extremely debilitating and chronic nature of Alzheimer's disease places a tremendous financial and social burden on family caregivers. These costs are frequently manifested in such areas as a) altered lifestyles including economic deprivation, lack of free time, and social isolation, b) psychological problems such as stress response syndrome, anxiety and depression, and c) stress-induced physical problems such as high blood pressure and peptic ulcers. These effects are often exacerbated by ignorance of the disease, small families or small dwellings, or the advanced age and frailty of the caregiver.

In the service of maintaining hope and preserving the self-esteem of their loved one, family members may deny and explain away the manifestation of troubling behavioral symptoms in the early stages of disease, waiting until quite late in the course of the illness to seek medical assistance. Such delaying tactics are especially unfortunate in cases where an early dementing illness can be reversed or the progress delayed with timely and appropriate medical care and compensatory activities. The elimination of ignorance about the disease and its early behavioral signs and symptoms might go far toward limiting the prevalence of disorders that mimic the early stages of Alzheimer's disease.

Multipronged psychological, sociobehavioral, and educational interventions not only help families to cope with day-to-day care of dementia patients but have also been shown to modify some disturbing behavioral problems in early and middle stages of the disease. Such things as carefully structured living environments, use of home support and respite services, information and other social supports, and training on how to solve problems and modify behavior can enable families to maintain Alzheimer's disease patients in the home for longer periods of time.

The physical and emotional strains of caring for an Alzheimer's disease patient are further exacerbated by a lack of financial and social and support services such as the absence of adequate reimbursement mechanisms to alleviate some of the financial burden and a dearth of community-based health and social services geared toward both the patient and the caregivers. While preliminary evidence supports the success of self-help groups, peer counseling, and individual psychotherapy in helping the caregiver to cope with his/her conflicted feelings and to manage the Alzheimer's disease at home, most communities lack such programs. Similarly, public services have traditionally been withheld from families who choose to retain a caregiving function as opposed to relinquishing care to an institution. Consequently, there is an urgent need to explore the potential value of such community-based programs as in-home supportive services, day-care programs designed especially for the Alzheimer's type patient, and respite-care beds that can be used on a daily, weekend, or periodic basis.

While most dementia patients live in community settings and are cared for by relatives, often the bulk of the burden falls on women--daughters, daughters-in-law, or wives who are aging themselves. However, radical shifts in sex roles in general and the rapidly increasing labor force participation of young and middle-aged women are likely to influence this pattern in the future. The change in obligations and family roles in coming years will significantly shape the nature and form of support relationships and arrangements for the demented over the course of the next half century.

Two primary factors that might contribute to eventual institutionalization are the lack of family caregivers and informal supports and/or the inability of families to cope for sustained periods of time with the behavioral problems and health-care needs of the patient in advanced stages of the disease. Preliminary findings in this area suggest that typically families can tolerate the cognitive impairment and disorientation that characterize the disease, but the secondary psychiatric symptoms constitute the "straws" that break the capacity and will of the family to provide care. Investigators have identified a number of symptoms, including incontinence, combativeness and violence, abrupt mood swings, catastrophic reactions, and overt sexual exposure that cause families the greatest stress in their caregiving activities.

Future Research Directions

While the family's key role in caring for the person with Alzheimer's disease is evident, the nature, dimensions, and impact of this role have yet to be determined. Much of the existing knowledge about the family as caregiver has been based either on anecdotal information that has not been substantiated by empirical evidence, or on extrapolations of findings from literature on the "frail" elderly, rather than on Alzheimer's disease patients per se. Furthermore, the research that has been conducted has been based primarily on retrospective and cross-sectional survey data. These studies are largely descriptive and have focused on the burden of family caregivers and/or the effectiveness of interventions as a means of reducing stress and helping families cope. A few prospective, community-wide epidemiological studies are underway that should begin to provide much-needed data on families and other social factors.

Consequently, a number of critical knowledge gaps exist that impede current understanding of the family as a caregiver. Baseline demographic information indicating how many families are affected, who they are, and where they are located is needed. Special attention should also be paid to such issues as the availability of family caregivers in the future; the role of the family in the early recognition of symptoms and the decision to seek medical care; the influence the family may have on the course of the disease; and how families use other social and health institutions. In addition, the motivating factors, barriers to providing care, and the actual financial and social costs incurred by the family and society remain to be more systematically specified. Finally, there has been a conspicuous absence of evaluation research concerning the relative cost-effectiveness of family and institutional care, as well as the impact of such interventions as educational material, family support groups, peer counseling, and individual and group psychotherapy.

Recommendations for the Development of Research

The most promising research directions include the following:

1. *Factors that assist the family to identify the problem.* This would include identification of factors that aid the family in the early recognition of symptoms and the decision to seek medical care, as well as the identification of the motivating factors making it possible for family members to assume and continue to play a primary caregiver role; identification of factors that persuade the family to relinquish care, and turn to institutionalization.

2. *Factors that assist the caregiver to cope.* This would include identification and evaluation of the most effective coping strategies and other psychological and socio-environmental interventions used by caregivers in supervising and

caring for the mildly, moderately, and severely demented individuals in noninstitutional settings. It would also focus on the efficacy of family support, individual and group psychotherapy, and peer counseling programs. Such research could also identify the kinds of information, education, and support that best reinforce and/or increase coping abilities of families caring for the Alzheimer's disease patient. Research on those family characteristics and interaction patterns that appear to be most amenable to caring for the Alzheimer's disease patient and most vulnerable to breakdown should also be initiated. Finally, systematic documentation and evaluation of the cost-effectiveness and efficiency of family care, and of informal and formal support services, would also be of significant use to family members.

3. *Factors affecting patients without families*: Exploration of innovative social support systems for patients with Alzheimer's disease who do not have any family.

Mechanisms for Implementation

In order to implement a research agenda that addresses the critical role of the family in caring for the Alzheimer's disease patient, the appropriate Federal institutes and agencies should collaboratively take the following steps:

1. Issue grant solicitations for and continue to support basic research to prepare a national profile of family caregivers.

2. Develop a competitive contract to evaluate the impact and cost-effectiveness of family care in conjunction with different kinds of institutional care, including the costs to society as well as to the patient and family.

3. Design research and demonstration project(s) to test the effectiveness of psychological, social, and environmental interventions (e.g., family support groups, peer counseling, professional mental and legal counseling) in assisting families in maintaining the Alzheimer's disease patient at home.

4. Conduct regional workshops involving representatives from a variety of disciplines including medicine, nursing, the behavioral sciences, social work, law, and recreational therapy.

5. Explore using the resources and energies of the members of the Alzheimer's Disease and Related Disorders Association to assist in data collection efforts with families nationwide.

6. Continue cooperative efforts among the NIA, NIMH, and NINCDS (with input from such agencies as AOA, VA, NCHSR, and NCHS) with: collaboration among scientists with multidisciplinary backgrounds; joint sponsorship of state-of-the-art conferences and workshops with broad dissemination of proceedings; joint issuance of program announcements for research and research training; and promotion of interagency agreements.

Chapter 7

Research on Systems of Care

Current Knowledge Base

Alzheimer's disease imposes large demands on the full range of long-term care services and facilities. Given the growing numbers of elderly in general, and especially the very old who are at greater risk for developing Alzheimer's disease, these demands will increase over the next several decades in the United States. Already, substantial proportions of health and social services to the elderly are utilized by persons with some form of dementia. Alzheimer's disease is a major predictor of institutionalization and accounts for as many as one-half of the elderly in long-term care settings. It appears that a larger number of older persons with Alzheimer's disease reside in the community than in institutions; both groups are affected by significant gaps in the development and orientation of the service system in meeting the special needs of Alzheimer's disease patients and their families.

At present, health, social, and personal care services in the community tend to be fragmented and often unresponsive or unavailable to Alzheimer's disease patients and their families. Institutional care for Alzheimer's disease patients is often characterized by a lack of thorough assessments, heavy reliance on convenient drug therapies for behavioral problems, and little attention to nonpharmacologic interventions that might help the patients and the family to cope. These problems are often compounded by a lack of staff at all levels trained for dealing with the symptoms and behavioral conditions associated with Alzheimer's disease.

Currently, we have some, but not yet sufficient, national statistics on institutional predictors and rates from both NCHS and NCHSR, as well as similar information from regional population studies. Information is also available on differences in health services utilization by gender, race, and SES factors. In addition to the insufficient epidemiological data, the lack of enough information about diagnosis, clinical course, treatment approaches, and family roles relating to Alzheimer's disease has interfered with the development of a clear, consistent rationale for a comprehensive, coordinated system of care for this disorder. Perhaps the most important aspect of the illness from a services perspective is that Alzheimer's disease is a progressive disorder, with a downward course leading to different service needs at different stages of the disease. Hence, attention must be given to a broad spectrum of services, ranging from the home to an institution. Moreover, the rate of decline as well as the nature and degree of disability vary greatly with different patients; hence, individual tailoring of services is needed and desirable.

Future Directions

There is a great need to understand better how the range of presently available services and settings--community-based and institutional--can best be designed, staffed, and coordinated with other services to deal with the different problems experienced by Alzheimer's disease patients and their families. Some definitions of terms may be helpful in this discussion, particularly with reference to services that may be considered in the long-term care of persons with Alzheimer's disease.

- *Long-term care* refers to the provision of care that draws upon a range of services addressing health, social, and/or personal care needs of individuals who can be in the community or an institution and who have disabilities that will continue for lengthy periods and require interventions or combinations of interventions over long time periods; chronic and progressive disorders typically lead to the involvement of the long-term care system for intermittent, indefinite, or continuous periods of time.

- *Comprehensive diagnostic and assessment services* refer to services that provide the patient with a thorough clinical evaluation, including attention to his or her health status, social functioning, and capacity to carry out everyday activities.

- *Case (care) management* refers to a mechanism for coordinating the efforts of the various service providers who are or should be involved around a specific clinical case; typically patients in need of a case management service have multiple service needs and lack the resources, capacity, or assistance to adequately engage and utilize these services; typically a case management service will provide an assessment of the patient, the development of a treatment plan, and monitoring of the patient's clinical course and utilization of other services.

- *In-home services* (examples):

  Home health services refer to services, supervised by a licensed health professional, that assist with simple health-related tasks such as monitoring the taking of medicines and personal care services such as getting out of bed, using the bathroom, bathing, dressing, eating, and exercising.

  Homemaker services refer to household assistance in such activities as shopping, picking up prescriptions, cooking, and cleaning.

- *Adult day care (programs)* refers to facilities providing health, social service, and personal care services for dysfunctional elderly individuals who do not need institutional placement; health is monitored, physical therapy may be available, activities are supervised, and meals and recreation are offered.

- *Partial hospitalization* refers to placement in a treatment facility for less than 24 hours each day services are provided; typically standard outpatient visits are not sufficient to treat the problem at hand, while full hospitalization is not necessary; extensive monitoring of a new drug or a change in dosage may require partial hospitalization for an impaired elderly patient.

- *Respite care* refers to temporary care provided for significantly impaired older persons in order to give caregivers in the family temporary relief to enable them to go on vacations or out of town. Respite care can be provided in the patient's home, in board and care or related facilities, in nursing homes, etc., and can vary in length of time from part of one day to a week or more.

- *Board and care facilities* refer to a wide range of facilities providing room and board with some form of protective supervision on a 24-hour basis (generally not nursing or medical care); some assistance in personal care activities of meal preparation, cleaning, laundry, bathing, and dressing is often available.

- *Institutional care* includes hospitals and nursing homes; nursing homes are in two forms--the skilled nursing facility and the intermediate care facility.

  The skilled nursing facility refers to a facility considered necessary for one who requires intensive, 24-hour-a-day supervision and treatment by a registered nurse.

> *The intermediate care facility* refers to a facility where 24-hour-a-day nursing by a registered nurse is not considered medically necessary, but where round-the-clock unskilled care is provided under the supervision of a registered nurse.

In order to plan for the most effective delivery of health and social services, accurate needs assessment studies must be conducted, focused on community-based and institutionalized groups of individuals with Alzheimer's disease. Several new large-scale epidemiologic catchment area studies are just beginning to develop a knowledge base, but national probability samples are necessary to provide unbiased representation of the U.S. population. Also, in order to tailor both community-based services and institutional care, more systematic and thorough means to assess cognitive, physical, and social function are required. Research to develop and implement assessment protocols needs to be further developed.

During the past few years, a variety of health and social services have been established to help avoid or delay institutionalization. Additional study should be focused on optimal approaches of outpatient clinical facilities in treating Alzheimer's disease patients; the effectiveness and costs of such alternatives as respite care, day programs, and home health services; and the care needs of older widowed or single women with Alzheimer's disease who live alone and of other populations at high risk for institutionalization.

In formal settings, a variety of health professionals and social service practitioners are caring for Alzheimer's disease patients. More research is needed on the optimal health care team and on training professionals to meet the health and social needs of patients and their caregivers.

We need to know more about factors that might influence the demand for and use of health services. To what extent are needs primarily determined by Alzheimer's disease as distinct from other coexisting conditions that might be amenable to treatment? Additional research should also focus on alternative health care delivery systems that can supplement-- rather than completely substitute for--family care. Health services research needs to examine the optimal mix between informal and formal care services and between institutional and noninstitutional formal services. Despite the availability of family and informal supports, most Alzheimer's disease patients will spend their last days in an institutional-care setting. We need to know how socio-environmental and organizational characteristics of long-term care settings (i.e., size, type of institution, staff/patient ratio) affect the functioning and well-being of Alzheimer's disease patients. Are new types of facilities, such as specialized intermediate care facilities, indicated for seriously impaired patients with Alzheimer's disease? How do staff attitudes about Alzheimer's disease affect their interactions with patients, and what effect does this have on patient morbidity or mortality?

Recommendations for Research

1. Study the range of community and institutional services relevant to Alzheimer's disease and related disorder patients in terms of their design, staffing, timing of use during the progression of the disorder, mix and coordination with other services, and costs. NCHSR, in addition to the programs represented on the Task Force, should be considered in this effort.

    - In addressing the needs of Alzheimer's disease patients, studies need to be done on how best to deliver such services as comprehensive assessment, case (care) management, outpatient treatment, home health care, respite care, adult day care (programs), partial hospitalization, and nursing home care.

    - Studies on the mix and coordination of different services for Alzheimer's disease patients should look not only at combinations of formal support system services provided by health care professionals, but also at the way these formal services can be combined with informal support system interventions provided by family, friends, and neighbors.

    - Research and development efforts should include attention to potential new services for Alzheimer's disease patients (e.g., should there be a specialized intermediate care facility for some with this disorder?).

    - Given the range of problems and interventions involved in planning services for Alzheimer's disease patients, particular attention should be placed on multidisciplinary backgrounds of researchers in this area.

2. Sponsor jointly state-of-the-art conferences and workshops with broad dissemination of proceedings, coordinating such efforts with programs represented on the Task Force along with NCHSR.

Chapter 8

Training: Research and Clinical

Current Review of Manpower and Training Issues

Currently, very little training from either a research or a clinical perspective focuses exclusively on Alzheimer's disease. Rather, since Alzheimer's disease is predominantly a disorder of the elderly, one is much more likely to find it subsumed within broader geriatric research and clinical training initiatives. Of course, attention to geriatric training is only a relatively recent phenomenon, gaining momentum since the late 1970s. Many reports, including that of the 1981 White House Conference on Aging, point out the large gaps between available geriatric personnel and training needs nationally and programs presently planned and underway. Secondary to marked shortages in trained geriatric personnel are shortages of those knowledgeable about Alzheimer's disease. Research training efforts in this area have undergone some growth, although the future of Federally supported clinical training initiatives is uncertain. Research training and clinical training are considered separately below.

Research Training

Despite increased awareness of the extent and burden of dementia in the elderly and despite very promising progress in research in the past few years, considerable growth is needed in programs designed to train investigators and academic leaders in this field. There is a serious shortage of persons trained and committed to research and teaching in all aspects of dementia, and there are too few settings in the nation with sufficiently qualified faculty to train the needed investigators.

Research training, support for investigators, and funding for research teachers are available through the various PHS institutes represented on the Task Force and through the VA and AOA to varying extents. Mechanisms of support include such awards as National Research Service Awards; Research Development, Teacher/Investigator Development, and Career Scientist Awards; and Geriatric Medicine and Geriatric Mental Health Academic Awards, as well as other training grants and fellowships.

Research training activities also take place within PHS supported clinical research centers, the VA's GRECC program, and AOA's Long-Term Care Gerontology Centers. The issues here are in terms of magnitude of training efforts in relation to geriatrics and Alzheimer's disease and in relation to neuroscience research training relevant to Alzheimer's disease. (For example, many feel that given the limited state of our knowledge regarding Alzheimer's disease, research training--either clinical or basic--should not be focused on Alzheimer's disease specifically; experience in biomedical research in general suggests that even were this targeting feasible, it might not be ultimately effective unless Alzheimer's disease were studied within broader biomedical, neuroscience, and behavioral science frameworks).

Clinical Training

A growing understanding of improved treatment/care/management practices around Alzheimer's disease is bringing about a reevaluation of clinical training needs and opportunities (see chapter on treatment). Efforts are focused primarily on geriatrics, with Alzheimer's disease being a part of the broader training programs. The primary programs are NIMH's Geriatric Mental Health Clinical Training Program, the VA's Geriatric Fellowship Program and GRECC's, AOA's Long-Term Care Gerontology Centers, and HRSA's Geriatric Education Centers. As with research training, the magnitude of the effort is modest. In addition, a number of clinical training target areas must be considered in conceptualizing a program to meet the needs of the field and the public. These areas include:

- Development of a training curriculum specifically targeted to treating persons with Alzheimer's disease and to providing consultation to other service providers working with Alzheimer's disease patients

- Attention to Alzheimer's disease in the basic training of clinical care providers potentially involved in the treatment of these patients (e.g., physicians, psychologists, nurses, social workers, etc.)

- Continuing education for those clinicians already in the field

- Specific service or setting training (e.g., training for carrying out a state-of-the-art diagnostic workup on a person suspected of having Alzheimer's disease; training for nursing home personnel in providing care for Alzheimer's disease patients; skill training for caregivers of Alzheimer's disease patients in the community)

- Training programs for families of Alzheimer's disease patients
- Training focused on special population needs, such as the poor and minorities with Alzheimer's disease
- Training for other groups of service providers likely to be involved in assisting Alzheimer's disease patients, such as clergy and lawyers.

Recommendations for Training: Research and Clinical

The Task Force recognizes that adequate training of investigators and academic leaders in all appropriate disciplines should be a high priority in order to advance research relevant to Alzheimer's disease and to conduct the extensive teaching needed by all professionals who have roles in diagnosing, treating, and caring for persons with dementia.

In November 1983, Assistant Secretary for Health Brandt established an interagency geriatric training committee within DHHS (the HHS Ad Hoc Committee on Enhancement of Training in Geriatrics and Gerontology), with representives from the Veterans Administration and other Federal programs, for purposes of coordinating and planning an overall geriatric training strategy that includes attention to research training and clinical training needs in the area of Alzheimer's disease.

The Task Force is reviewing the findings and recommendations of this interagency geriatric committee in order to better coordinate training initiatives across the Department and the VA relevant to Alzheimer's disease.

1. The development of training programs utilizing the already existing mass of faculty/investigators in the field should be encouraged; current training programs with a broader geriatric and/or neuroscience thrust could be enhanced while examining ways in which their focus on Alzheimer's disease could be strengthened, with new training programs being initiated in areas where gaps continue. Support should also be provided for career development for faculty/investigators who are capable of proceeding more independently in education and research in areas that would have relevance to Alzheimer's disease.

2. The feasibility of developing model programs in the seven clinical/services training target areas delineated above should be examined, with appropriate resources considered. The recommendations of the 1981 White House Conference on Aging should be consulted in this regard.

Chapter 9

Educational Materials and Information Dissemination

Description of Need

We are witnessing the rapid development of new questions and answers about Alzheimer's disease. Accordingly, new information needs to be regularly transmitted and outdated ideas dispelled. Emerging clues to understanding better the cause, course, and treatment of the disorder need to be rapidly and effectively conveyed; results of studies leading to dead-ends and ineffective treatments must also be communicated to professionals and the public alike.

In the process of specifying categories of needed information, target groups of individuals to receive such information must also be identified. Researchers, service providers, policymakers, reporters, the general public, and affected individuals and families all need to be considered. Depending on the stage of the illness, the family has varying needs for information. They need to know what questions to ask during the diagnostic workup and how to determine whether their doctor is providing good medical care. They need to know what to expect in terms of changes in personality and behavior as Alzheimer's disease progresses. They also need help in interpreting the latest research findings as they are reported in the popular press. Most importantly, they need information on how to cope with a relative who has the disease. Health care professionals need to know the very latest information on diagnosis, course, and possible treatments of the disease. They also need to know about support systems that are available to help the family cope with the problems. The model of the geriatric medical team (including physicians, nurses, and social workers) is particularly useful in dealing with the Alzheimer's disease family. Policymakers need to know more about the extent, impact, and cost of Alzheimer's disease; about opportunities for medical advances and cost savings; and about future needs. Reporters need timely information in all of these areas as well as help from experts in interpreting the significance of research results.

Current Sources

The PHS has been active in developing several useful fact sheets and pamphlets on Alzheimer's disease that have been of particular interest to families and practitioners (several of these have been reprinted and distributed by the Alzheimer's Disease and Related Disorders Association). Moreover, proceedings from research conferences and workshops sponsored by NIA, NIMH, NINCDS, and the VA have been published by private companies resulting in at least six state-of-the-art books, in as many years, of major interest to investigators.

Meanwhile, an increasing number of articles on Alzheimer's disease are appearing in scientific journals as well as the popular press. New texts and book chapters by professionals in the field are also appearing for clinicians, while a book titled *The 36-Hour Day* has become a classic for families. Moreover, the national office and local chapters of the Alzheimer's Disease and Related Disorders Association have been particularly active in disseminating information to families on how to cope with Alzheimer's disease.

Despite these multiple and diverse sources of information, new developments quickly outdate many of these publications and keep demand high. In addition, various literature gaps exist. Published curricula for training different groups of providers are sparse. Similarly, literature geared to management or intervention strategies in specific settings such as senior citizen housing and nursing homes is deficient. Meanwhile, treatment approaches that are effective in alleviating excess disability in Alzheimer's disease patients and in maximizing quality of life remain underappreciated and need to be much better described for both practitioners and the public. It would also be useful to have information on quack cures and experimental therapies, treatment centers, service programs, and reimbursement policies. Another goal might be to develop and maintain a current general listing of publications and other information resources as well as a listing of audiovisual resources.

Recommendations

1. The information offices of the Department and other Federal agencies represented on the Task Force should distribute all informational materials on Alzheimer's disease developed by each Federal program.

2. The Task Force should oversee the preparation of two new pamphlets on Alzheimer's disease—one addressed to the practitioner, the other addressed to the family.

3. Voluntary agencies should be encouraged to assist in the processes of disseminating information and developing new educational materials as addressed in the aforementioned two recommendations.

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APPENDIX

PROJECTS ON ALZHEIMER'S DISEASE SUPPORTED BY FEDERAL PROGRAMS

Administration on Aging
Grants Relating to Alzheimer's Disease

Active as of October 31, 1983

The Long Term Care Gerontology Centers sponsored by the Administration on Aging (AOA) are engaged in a variety of activities relating to long-term care concerns. A number of the Center activities have a direct or an indirect bearing on the following aspects of Alzheimer's disease: epidemiology, treatment, family, and systems of care.

It should be noted that Long Term Care Gerontology Center projects are not awarded on the basis of categories of medical diagnosis. Instead, they address the subject of Alzheimer's disease as a major subcategory of long-term care concerns. Listed below are the Centers that have activities that specifically relate to Alzheimer's disease. Under the name of the Center are listed the relevant categories addressed by that particular Center.

Sidney Katz, M.D.
Southeastern New England Long-Term Care Gerontology Center
Brown University, Providence, R.I.
90-AT-2164; $573,344
1. Epidemiology; 5. Treatment; 6. Family.

Barry J. Gurland, M.D.
Center for Geriatrics and Gerontology/Long Term Care
Columbia University, New York, N.Y.
90-AT-2155; $573,695
1. Epidemiology; 3. Diagnosis; 5. Treatment; 6. Family;
7. Systems of Care.

Evan Sorber, Ed.D.
Mid-Atlantic Long Term Care Gerontology Center
Temple University, Philadelphia, Pa.
90-AL-0011; $512,000
6. Systems of Care.

Eric Pfeiffer, M.D.
Suncoast Gerontology Center for Health and Long Term Care
University of South Florida, Tampa, Fla.
90-AT-2157; $573,698
3. Diagnosis; 4. Clinical Course; 5. Treatment; 6. Family;
7. Systems of Care.

Frederick Tavill, M.D.
Long Term Care Gerontology Center
Medical College of Wisconsin, Milwaukee, Wis.
90-AL-0010; $514,985
1. Epidemiology; 3. Diagnosis; 6. Family; 7. Systems of Care.

Theodore H. Koff, Ed.D.
Long Term Care Gerontology Center
University of Arizona, Tucson, Ariz.
90-AT-2166; $514,898
4. Clinical Course; 7. Systems of Care.

Russell C. Mills, Ph.D.
Long Term Care Gerontology Center
University of Kansas, Kansas City, Kans.
90-AT-2154; $476,659
3. Diagnosis; 5. Treatment; 6. Family; Systems of Care.

John Beck, M.D.
UCLA/USC Long Term Care Gerontology Center
University of California, Los Angeles, Calif.
90-AT-2167; $573,521
2. Etiology and Pathogenesis; 5. Treatment; 6. Family.

Maureen M. Henderson, M.D.
Pacific Northwest Long Term Care Center
University of Washington, Seattle, Wash.
90-AT-2152; $573,553
1. Epidemiology

National Institute on Aging
Grants Relating to Alzheimer's Disease

Active as of October 31, 1983

1. Epidemiology

Barry Reisberg, M.D.
New York University, New York, N.Y.
Aging and Dementia: Longitudinal Course of Subgroups
R01 AG-03051-01; $127,686

Dennis A. Evans, M.D.
Peter Bent Brigham Hospital, Boston, Mass.
Senile Dementia: Natural History
N01 AG-12106; $399,912

Interagency agreement with:
National Heart, Lung, and Blood Institute
Investigate Senile Dementia in Framingham Heart Study
Y02 AG-20040; $80,000

Interagency agreement with:
National Institute of Mental Health
Catchment Area Study of Senile Dementia
No new funding for FY 83
Y01 AG-90020; (total thru FY 79-80 $835,000)

2. Etiology and Pathogenesis

NIA Intramural Program
Brain Function in Aging and Dementia
Blood-Brain Barrier Function
Lipid and Protein Biochemistry of the Brain
Down Syndrome-Biochemical Defect in Relation to Dementia and Disturbed Brain Function
$2,648,000 (4 studies)

Shu-Hui C. Yen, Ph.D.
Yeshiva University, New York, N.Y.
The Aging Brain: Immunohistology and Biochemistry
K04 AG-00028-05; $40,338

Charles A. Marotta, Ph.D.
McLean Hospital Division of Massachusetts General
Age-Related Changes in Central Nervous System Fibrous Proteins and Messenger Riobio Nucleic Acid
K04 AG-0084-03

Ira R. Katz, M.D.
Medical College of Pennsylvania, Philadelphia, Pa.
Hypoxia and Neurotransmitters: Relevance to Aging
K04 AG-00085-03; $40,176

Dike N. Kalu
University of Texas
Aging and Calcium Metabolism Control
R01 AG-00345-03; $34,238

Avis L. Sylvia
Duke University
Brain Function and Oxidative Metabolism During Aging
R01 AG-00517-06; $115,796

Raymond J. Lasek, Ph.D.
Case Western Reserve University, Cleveland, Ohio
Aging Changes in Neuronal Structure and Function
P01 AG-00795-05; $482,070

John R. Sladek, Jr., Ph.D.
University of Rochester, Rochester, N.Y.
Aging: Effects on Peptidergic and Aminergic Neurons
R01 AG-00847-04; $116,965

Peter Davies
Yeshiva University, New York, N.Y.
Aging and Dementia: Cholinergic Neuron Biochemistry
R01 AG-01066-03; $117,279

Paul D. Coleman, Ph.D.
University of Rochester, Rochester, N.Y.
Computer Aided Study of Dendrites in Aging Human Brain
R01 AG-01121-05; $63,361

Shu-Hui C. Yen, Ph.D.
Yeshiva University, New York, N.Y.
The Aging Brain: Immunohistology and Biochemistry
R01 AG-01136-05; $71,300

Dennis J. Selkoe, M.D.
McLean Hospital Division of Massachusetts General
Aging in the Brain: Role of the Fibrous Proteins
RO1 AG-01307-03A1; $161,749

Daniel P. Perl, M.D.
University of Vermont and State Agricultural College
Trace Elements in Aged Neurons and Senile Dementia
RO1 AG-01415-04; $125,866

Leonard M. Schuman, M.D.
University of Minnesota and Minneapolis-St. Paul
Epidemiologic Study of Alzheimer's Disease
RO1 AG-01529-04; $52,200

Dean O. Smith, Ph.D.
University of Wisconsin, Madison, Wis.
Synaptic Structure and Function During Senescence
RO1 AG-01571-04; $63,855

Philip W. Landfield, Ph.D.
Wake Forest University, Winston-Salem, N.C.
Neurophysiological Studies of Brain Aging
R01 AG-01737-04; $49,244

William O. McClure, Ph.D.
University of Southern California, Los Angeles, Calif.
Neuroleptics, Aging, and Cholinergic Function
R01 AG-01896-03; $75,894

Mary L. Michaelis, Ph.D.
University of Kansas, Lawrence, Kans.
Adenosine as a Metabolic Autoregulator in Aging Brain
R23 AG-01948-03; $38,453

Peter D. Gorevic
State University of New York, Stony Brook
Senile Amyloidosis: Biochemistry and Immunohistochemistry
R01 AG-01973-03; $38,233

Marilyn M. Sanders
Rugters Medical School
Gene Control and Cyclic Guanosine Monophosphate (cGMP) in Drosophilia and Senile Dementia
R01 AG-02066-03; $91,295

Burton L. Shapiro
University of Minnesota
Cystic Fibrosis and Fibroblasts: Intracellular Calcium
R01 AG-02114-03; $72,552

Charles A. Marotta, Ph.D.
McLean Hospital Division of Massachusetts General

Program Project: Molecular Biology of Neuronal Aging
P01 AG–02126–03; $217,721

Stanley B. Prusiner, M.D.
University of California, San Francisco, Calif.
Viral Degenerative and Dementing Diseases in Aging
PO1 AG–02132; $212,039

Kenneth L. Davis
Mount Sinai School of Medicine
Cholinergic Treatment of Memory Deficits in the Aged
PO1 AG–02219–03; $220,672

Charles F. Howard, Jr.
Medical Research Foundation of Oregon
Age–Dependent Changes in Glucose Tolerance
RO1 AG–02281–03; $72,300

Cameron J. Camp
Fort Hays State University
Aging and Memory: Fact Retrieval Versus Inference
RO1 AG–02427–02; $14,283

Leah L. Light
Pitzer College
Contextual and Semantic Memory Processing in Old Age
RO1 AG–02452–03; $66,558

Robert Katzman
Yeshiva University
Senile Dementia: Alzheimer and Vascular
PO1 AG–02478–03; $806,708

Maurice M. Rapport
New York State Psychiatric Institute
Membrane Pathology in Aging and Senile Dementia
R01 AG–02496–02; $85,375

Robert A. Floyd
Oklahoma Medical Research Foundation
Neurotransmitters and Oxidative Damage in Aging Brain
RO1 AG–02599–02; $63,302

Anne B. Johnson
Yeshiva University
Pathogenesis of Senile Dementia and Cerebral Aging
RO1 AG–02650–03; $77,762

Stephen J. Buell
University of Rochester, Rochester, N.Y.
Quantitative Study of Dendrites in Aging and Dementia
RO1 AG-02680-02; $81,660

Darlene V. Howard
Georgetown University
Studies of Aging, Semantic Processing, and Memory
RO1 AG-02751-02; $36,189

Vlasta K. Zbuzek
University of Medicine and Dentistry of New Jersey
Vasopressin (VP) and Aging
RO1 AG-02778-01; $105,551

Richard P. Mayeux
Columbia University
Depression and Parkinson Disease: A Model in Aging
R23 AG-02802-02; $49,986

Melvyn J. Ball
University of Western Ontario
Clinical and Pathological Study of Alzheimer's Disease
RO1 AG-03047-02; $252,911

Elias E. Manuelidis
Yale University
Aminal Models for the Study of Dementias and Aging
PO1 AG-03106-01A1; $349,478

Thomas H. McNeill
University of Rochester, Rochester, N.Y.
Histochemical Studies of the Aged Basal Ganglia
R23 AG-03254-01; $53,306

Caleb E. Finch
University of Southern California
Aging and Dopaminergic Regulation
PO1 AG-03272-01; $256,458

Donald L. Price
Johns Hopkins University
Alzheimer's Disease: Nucleus Basalis/Cholinergic Defect
RO1 AG-03359-01; $159,654

Frank Morrell
Rush-Presbyterian-St. Luke's Medical Center
Neurobiology of Age-Related Deficit in Memory
RO1 AG-03410-01; $113,055

Samuel Gershon
Wayne State University
Cholinergic and Cerebrovascular Functions in Aging
RO1 AG-03571-01; $125,001

Richard E. Galardy
University of Kentucky
Choline Acetyltransferase in Alzheimer's Disease
RO3 AG-03605-01; $20,372

Richard F. Ochillo
Xavier University of Louisiana
Cholinergic Muscarinic Receptor and Aging
RO1 AG-03674-01; $19,985

Charles B. Nemeroff
University of North Carolina, Chapel Hill
Neuropeptides in Senile Dementia of the Alzheimer Type
R03 AG-03701-01; $18,862

Andre Dray
University of Arizona
Adrenergic-Cholinergic Actions Related to Dementia
R03 AG-03717-01; $15,570

Robert H. Lenox
University of Vermont and State Agricultural College
Muscarinic Receptor Subtypes: Tools for Aging Research
R03 AG-03720-01; $21,446

Fulton T. Crews
University of Florida
Age Dependent Changes in Synaptosomal Membrane Fluidity
R03 AG-03736-01; $20,476

Norman Weiner
University of Colorado Health Sciences Center
Brain Mondamines, Protein Phosphorylation, and Aging
RO1 AG-03932-01; $99,519

Gary E. Gibson
Burke Rehabilitation Center
Neurotransmitter and Energy Metabolism
RO1 AG-04171-03; $96,634

Alane S. Kimes
Baltimore City Hospitals
Kinetic Studies of the Blood Brain Barrier
F32 AG-05183-03; $16,236

Alane S. Kimes
Baltimore City Hospitals
Kinetic Studies of the Blood Brain Barrier
F32 AG-05182-03S1; $1,255

Kenneth S. Kosik
McLean Hospital Division of Massachusetts General
Cholinergic Activity and Axoplasmic Transport
F32 AG-05268-02; $20,892

3. Diagnosis

NIA Intramural Program
Brain Function in Aging and Dementia
Characterizing and Diagnosing Alzheimer's Disease
Development of New CT Techniques for Evaluating and Diagnosing SDAT
Biological Markers of Alzheimer's Disease
$2,648,000 (4 studies)

Marvin A. Oleshansky
New York University
Serum Dopamine Beta Hydroxylase (DBH) and Organic Brain Syndromes of the Elderly
K08 AG-00065-03; $48,341

Jacob H. Fox
Rush University
Cerebral Decline in Aging
PO1 AG-00905-05; $162,335

Lorne K. Direnfeld
Boston University
Parkinson's Disease and Dementia
K08 AG-00152-02; $46,045

Myrna F. Schwartz
University of Pennsylvania
Patterns of Cognitive Deficit in Alzheimer's Disease
RO1 AG-02231-04; $169,175

Robert Katzman
Yeshiva University
Senile Dementia: Alzheimer and Vascular
PO1 AG-02478-03; $806,708

Melvyn J. Ball
University of Western Ontario

Clinical and Pathological Study of Alzheimer's Disease
RO1 AG-03047-02; $252,911

Donald L. Price
Johns Hopkins University
Alzheimer's Disease: Nucleus Basalis/Cholinergic Defect
RO1 AG-03359-01; $159,654

Donald Kaye
Philadelphia Geriatric Center-Friedman Hospital
Teaching Nursing Home Award
PO1 AG-03934-01; $896,204 (3 studies)

Robert Katzman
Yeshiva University
Teaching Nursing Home
P01 AG-03949-01; $758,978 (3 studies)

4. Clinical Course

Anderson D. Smith
Georgia Institute of Technology
Interaction Between Human Aging and Memory
RO1 AG-00445-08; $35,997

Myrna F. Schwartz
University of Pennsylvania
Patterns of Cognitive Deficit in Alzheimer's Disease
RO1 AG-02231-04; $169,175

Sandra Weintraub
Beth Israel Hospital
Reversible Changes of Cognition in the Elderly
PO1 AG-02269-03; $156,325

Richard P. Mayeux
Columbia University
Depression and Parkinson Disease: A Model in Aging
R23 AG-02802-02; $49,986

Leonard W. Poon
Massachusetts General Hospital
Cognitive Deficit Identification in Dementia
RO1 AG-03354-01; $87,959

Dennis A. Evans, M.D.
Peter Bent Brigham Hospital
Senile Dementia: Natural History
N01 AG-12106; $399,912

Interagency agreement with:
National Heart, Lung, and Blood Institute
Investigate Senile Dementia in Framingham Heart Study
Y02 AG-20040; $80,000

Interagency agreement with:
National Institute of Mental Health
Catchment Area Study of Senile Dementia
No new funding for FY 83
Y01 AG-90020; (total thru FY 79-80 $835,000)

5. Treatment

Kenneth L. Davis
Mount Sinai School of Medicine
Cholinergic Treatment of Memory Deficits in the Aged
PO1 AG-02219-03; $220,672

Larry E. Tune
Johns Hopkins University
Neuroleptic Drug Level Monitoring in Dementia Syndromes
R03 AG-3672-01; $20,850

Donald Kaye
Philadelphia Geriatric Center-Friedman Hospital
Teaching Nursing Home Award
PO1 AG-03949-01; $758,978

Robert Katzman
Yeshiva University
Teaching Nursing Home
PO1 AG-03949-01; $758-978

8. Training of Research and Clinical Personnel

F. Stephen Vogel
Duke University
Biological Approaches to Dementia
T32 AG-00007-08; $57,124

Shu-Hui C. Yen
Yeshiva University
The Aging Brain: Immunohistology and Biochemistry
K04 AG-00028-05; $40,338

Stanley H. Appel
Baylor College of Medicine
Biological Approaches to Dementia
T32 AG-00061-05; $33,850

Marvin A. Oleshansky
New York University
Serum Dopamine Beta Hydroxylase (DBH) and Organic Brain Syndromes of the Elderly
K08 AG-00065-03; $48,341

Charles A. Marotta
McLean Hospital Division of Massachusetts General
Age-Related Changes in Central Nervous System Fibrous Proteins and Messenger Ribio Nucleic Acid
K04 AG-00084-03; $38,718

Ira R. Katz
Yeshiva University
Hypoxia and Neurotransmitters: Relevance to Aging
K04 AG-00085-03; $40,176

Lorne K. Direnfeld
Boston University
Parkinson's Disease and Dementia
K08 AG-00152-02; $46,045

Alane S. Kimes
Baltimore City Hospitals
Kinetic Studies of the Blood Brain Barrier
F32 AG-05183-03; $16,236

Alane S. Kimes
Baltimore City Hospitals
Kinetic Studies of the Blood Brain Barrier
F32 AG-05183-03S1; $1,255

Kenneth S. Kosik
McLean Hospital Division of Massachusetts General
Cholinergic Activity and Axoplasmic Transport
F32 AG-05268-02; $20,892

9. Educational Materials and Information Dissemination

James D. Watson
Cold Spring Harbor Laboratory
Conference on Biological Aspects of Alzheimer's Disease
R13 AG-03540-01; $30,672

National Institute of Allergy and Infectious Diseases Grants Relating to Alzheimer's Disease

Active as of October 31, 1983

The National Institute of Allergy and Infectious Diseases supports research on the biology and epidemiology of latent and slow viruses. The Panel on Persistent Viral Infections of the NIAID Virology Task Force devoted a chapter of its 1979 report (Volume 3) to Spongiform Encephalopathy Agents. Their summary stated:

> The major problems are characterizing the agents and finding a rapid method of quantitating infectivity. Logically these studies would concentrate on scrapie in mice as the most readily studied spongiform encephalopathy. Explanation of the novel physical chemical properties, the failure to visualize by electron microscopy, the association with membranes, and the lack of immunogenicity will probably only be explained after these biochemical problems are solved. Furthermore, studies of possible vertical transmission, mode of replication, mechanisms of cytopathic pathology, explanation of restriction of lesions of CNS, mode of natural spread of Creutzfeldt-Jacob disease, and the possible methods of prevention or treatment will probably not be feasible until the nature of the agents is better understood and a more effective method of detecting them is in hand.

Accordingly, the NIAID studies described here are aimed at resolutions of these unknowns.

W. J. Hadlow
RML, Epidemiology Branch, NIAID
Relation of Viruses to the Genesis of Chronic Diseases
Z01 AI-00082-21; $199,012

Duard L. Walker
University of Wisconsin, Madison
Study of a New Human Papovavirus
RO1 AI-11217-10; $150,481

Leonard C. Norkin
University of Massachusetts, Amherst
An SV 40–Rhesus Monkey Cell Persistent Virus
RO1 AI–14049–06; $77,133

Howard L. Lipton
Northwestern University
Theiler's Virus - Induced Demyelinating Disease
RO1 AI–14139–06; $102,217

Harry O. Openshaw
University of California, Davis
HSV Brain Stem Infection: Latency and Reactivation
R23 AI–17065–02; $37,726

Susan R. Weiss
University of Pennsylvania
Coronaviruses: Molecular Biology and Persistence
RO1 AI–17418–02; $111,027

Martin G. Myers
Children's Hospital Medical Center, Cincinnati, Ohio
Pathophysiology of Varicella Zoster Virus Infection
RO1 AI–18847–02; $92,515

Charles J. Pfau
Rensselaer Polytechnic Institute
Maintenance of Persistent Murine LCM Virus Infection
RO1 AI–16562–02; $70,489

David D. Porter
University of California, Los Angeles
Slow Virus Infections: Immunologic and Viral Studies
RO1 AI–09476–13; $91,473

Raymond M. Welsh, Jr.
University of Massachusetts Medical School
Defective Virus, Immunity and Chronic Disease
RO1 AI–17672–03; $129,071

Raymond M. Welsh, Jr.
University of Massachusetts Medical School
Maintenance of Chronic Virus Disease
K04 AI–00432–05; $37,781

National Institute of Mental Health Grants Relating to Alzheimer's Disease

Active as of October 31, 1983

1. Epidemiology

NIMH Epidemiologic Catchment Area Program
$930,000

2. Etiology and Pathogenesis

Joseph T. Coyle, M.D.
Johns Hopkins University, Baltimore, Md.
Neuropsychiatric Disorders: Selective Neural Loss
R01 MH-00125; $183,750

Peter Davies, Ph.D.
Albert Einstein College of Medicine, Bronx, N.Y.
Aging and Dementia: Cholinergic Neuron Biochemistry
R01 MH-38623; $214,824

Lissy F. Jarvik, M.D.
University of California, Los Angeles, Calif.
Alzheimer Type Dementia: A Biobehavioral Family Study
R01 MH-36205; $800,892

Marlyne Kilbey, Ph.D.
Middle Tennessee State University, Murfreesboro, Tenn.
Age Effects in Animal Models of Abnormal Behavior
RO1 MH-34277; $30,278

James M. Puckett, Ph.D.
S. West Missouri State University, Springfield, Mo.
Age Differences in Decay Rates
R03 MH-38057; $14,872

Charles F. Reynolds, III, M.D.
Western Psychiatric Institute and Clinic, Pittsburgh, Pa.
EEG Sleep, Aging and Mental Illness
RO1 MH-37869; $133,700

(also see: P. Prinz, 3.)

3. Diagnosis

Elizabeth O. Clark, Ph.D.
Brentwood VA Medical Center, Los Angeles, Calif.
Tests of Logic and Inference in Alzheimer Type Dementia
RO1 MH-38659; $55,432

Steven H. Ferris, Ph.D.
New York University, New York, N.Y.
Mental Health in Aging: Drug Effects on Brain
RO1 MH-38274; $228,138

Steven H. Ferris, Ph.D.
New York University, New York, N.Y.
Neurometric Assessment of Mental Health in Aging
RO1 MH-32577; $371–419

Eric B. Larson, M.D., MPH
University of Washington, Seattle, Wash.
Dementia and Mental Health in the Aged
R01 MH-33841; $111,610

George Niederehe, Ph.D.
Texas Research Institute of Mental Sciences, Houston, Tex.
Memory Impairment in Affective Disorders of the Aged
RO1 MH-30644; $89,113

Patricia Prinz, Ph.D.
University of Washington, Seattle, Wash.
Sleep/Waking Patterns in Dementia
RO1 MH-33688; $231,739

Barbara H. Stanley, Ph.D.
Wayne State University, Detroit, Mich.
Informed Consent in Aged Psychiatric Patients
RO1 MH-37983; $196,900

Walter Riege, Ph.D.
VA Hospital, Sepulveda, Calif.
Non-Verbal Memory in the Aged Mentally Healthy or Ill
RO1 MH-32172; $91,058

Bart P. Vrtunski, Ph.D.
Case Western Reserve University, Cleveland, Ohio
Psychomotor Slowing and Age: Microbehavioral Analysis
RO1 MH-33181; $81,185

NIMH Intramural Program
Differential Diagnosis and Memory

(also see: A. George, M.D., 4; L. Jarvik, 2; I. Katz, 5;
B. Reifler, 5)

4. Clinical Course

Ajax E. George, M.D.
New York University, New York, N.Y.
Mental Health, Brain Impairment and Aging
RO1 MH-36969; $380,951

Robert J. Nathan, M.D.
Hahnemann Medical College, Philadelphia, Pa.
Aging: Brain Structures and Sociobehavioral Variables
RO1 MH-37281; $186,411

Erdman S. Palmore, Ph.D.
Duke University, Durham, N.C.
Mental Illness and Social Support Among the Very Old
RO1 MH-33704; $345,000

George E. Vaillant, M.D.
Harvard University, Cambridge, Mass.
Effect of Mental Health on Aging
RO1 MH-32885; $361,021

(also see: G. Niederehe, 6; P. Prinz, 3; B. Reifler, 5; I. Katz, 5).

5. Treatment

Jonathan O. Cole, M.D.
Boston Mental Health Foundation, Inc.
Lecithin in Senile Dementia
RO1 MH-33699; $125,000

Suzanne H. Corkin, Ph.D.
Massachusetts Institute of Technology, Cambridge, Mass.
Lecithin Precursor Treatment in Alzheimer's Disease
RO1 MH-32724; $255,654

Steven H. Ferris, Ph.D.
New York University, New York, N.Y.
Psychopharmacology of Neurotransmitter Systems in Aging
RO1 MH-29590; $534,592

Ira R. Katz, M.D.
Yeshiva University, Bronx, N.Y.
Mental Health and Aging: Delineation of Depression
RO1 MH-37026; $321,676

Burton T. Reifler, M.D.
University of Washington, Seattle, Wash.
Mental Health in the Aged: Combined Dementia and Depression
RO1 MH-36596; $233,698

Barry Reisberg, M.D.
New York University Medical Center, New York, N.Y.
Opioid Antagonist Treatment of Alzheimer's Disease
RO1 MH-38275; $142,117

Richard I. Shader, M.D.
Boston, Mass.
Applications of Pharmacokinetics in Clinic Psychiatry
RO1 MH-34223; $250,000

Jared Tinklenberg, M.D.
Stanford University, Stanford, Calif.
Neuropeptides, Mood, and Memory in the Elderly
RO1 MH-36609; $163,553

NHBLI-NIMH Pilot Study of Systolic Hypertension
$450,000

NIMH Intramural Program
Drug Intervention Studies with Scopolamine; Lecithin and Anticholinesterase; DDAVP; Flouride

(also see: E. Larson—3)

6. The Family

Joseph Becker, Ph.D.
University of Washington, Seattle, Wash.
Stress Vulnerability in Alzheimer's Patients' Families
RO1 MH-33779; $231,542

George Niederehe, Ph.D.
Texas Research Institute of Mental Sciences, Houston, Tex.
Family Dynamics and the Care of Aged with Dementia
RO1 MH-35400; $199,853

Walter E. Poulshock, Ph.D.
Benjamin Rose Institute
Caring for Elders and Mental Health of Family Members
RO1 MH-35360; $300,000

Joanne Steuer, Ph.D.
University of California, Los Angeles, Calif.

Support Groups for Families of Dementia Patients
RO1 MH-37053; $44,650

Steven H. Zarit, Ph.D.
University of Southern California, Los Angeles, Calif.
Family Interventions for Senile Dementia
RO1 MH-34507; $267,000

(also see J. Barbaccia, 2; E. Brody, 2; L. Jarvik, 2)

7. Systems of Care

J. Barbaccia, M.D.
UCSF
Adjustment of Older Persons After Acute Hospitalization
RO1 MH-32731; $70,000

Elaine M. Brody, M.S.W.
Philadelphia Geriatric Center, Philadelphia, Pa.
Women, Work and Care of the Aged: Mental Health Effect
RO1 MH-35352; $318,000

Carl I. Cohen, M.D.
New York University, N.Y.
Old Men on the Bowery in the 1980's: Adaptive Strategies
RO1 MH-35724; $155,050

M. Powell Lawton, Ph.D.
Philadelphia Geriatric Center, Philadelphia, Pa.
The Last Year of Life: Mental Health Aspect
RO1 MH-37707; $289,968

(also see: W. Poulshock, 6)

8. Training of Research and Clinical Personnel

NIMH initiated in Fiscal Year 1983 a new teacher investigator award program called the Geriatric Mental Health Academic Award Program, with eight awards being made in Fiscal Year 1983- four to psychiatrists and four to nurses. The purpose of this award is to assist in the development of a research-oriented resource person in geriatric mental health in academic settings. The broad areas addressed by these scientists include that of Alzheimer's disease. $482,284

NIMH initiated in Fiscal Year 1983 a new 3-part clinical training program in Mental Health and Aging. Fifty awards were made to the four core mental health disciplines, with a focus on the development of teachers as well as attention to those in general training. The range of areas addressed in the curricula of these programs included attention to Alzheimer's disease. $2,250,000

9. Educational Materials and Information Dissemination

An active dissemination-of-information program on Alzheimer's disease is carried out by NIMH. Efforts include the distribution of a Fact Sheet on Alzheimer's disease written especially for families, the dissemination of research findings about Alzheimer's disease in research summaries printed by NIMH, and the writing of textbook chapters and editing of books on Alzheimer's disease by NIMH staff for researchers and clinicians in the field.

National Institute of Neurological and Communicative Disorders and Stroke Grants Relating to Alzheimer's Disease

Active as of October 31, 1983

1. Epidemiology

B. Schoenberg
OD/IRP/NINCDS
Epidemiology of Dementia
Z01 NS-02240-06; $196,412

B. Schoenberg
OD/IRP/NINCDS
Racial Differentials in the Prevalence of Major Neurologic Disorders and Surveys in Developing Countries
(10% of total)
Z01 NS-02370-04; $72,018

2. Etiology and Pathogenesis

M. Baudry
University of California, Irvine
Pyruvate Dehydrogenase and Neuropathology
RO1 NS-18427-02; $52,670

W. Beierwaltes
University of Michigan
PETT Study and Biochemistry and Metabolism of the CNS
(10% of total award)
P01 NS-15655-04; $87,274

S. Brady
Case Western Reserve
Aging Changes in Subclasses of Neuronal Tubulin
R23 NS-18361-02; $51,834

R. Broadwell
University of Maryland

The Blood-Brain Barrier in Normal and Dimethyl Sulfoxide (DMSO)-Treated Brain
RO1 NS-18030-02; $95,703

T. N. Chase
ET/IRP/NINCDS
Pharmacology, Biochemistry and Physiology of Central Neurotransmitters
R01 NS-02265-06; $360,089

H. Coulter
University of Minnesota
Neuropeptide Immunocytochemistry of Frozen-Dried Brain
R01 NS-18428-02; $74,532

J. Coyle
Johns Hopkins Medical School
Cortical Cholinergic Lesion/Model for Alzheimer Dementia
RO1 NS-18414-02; $101,015

L. DeBault
University of Oklahoma
Vascular Endothelium Form and Function—Effects of Glia
R01 NS-18775-02; $80,759

G. DiChiro
SNB/IRP/NINCDS
Positron Emission Tomography
(50% of total)
Z01 NS-02315-06; $114,574

L. Dokas
Medical College of Ohio, Toledo
Corticosterone and RNA Metabolism in the Hippocampus
RO1 NS-17118-03; $55,252

J. Duerre
University of North Dakota
Brain Histone Methylases
RO1 NS-09725-10; $57,090

G. Entine
Radiation Monitoring Devices, Inc., Mass.
Crystal Identification Sensors for PET Imaging
(10% of total award)
R43 NS-20409-01; $10,339

R. Fisher
Johns Hopkins University

Conference for Young Neurological Investigators
R13 NS-18890-01; $7,500

W. Frey
St. Paul-Ramsey Medical Center
The Role of GTPase in Human Brain
RO1 NS-14583-05; $90,759

C. Gajdusek
CNSS/IRP/NINCDS
Chronic CNS Disease Studies: Slow Latent and Temperate Virus Infections
(10% of total)
Z01 NS-00969-18; $157,130

F. Gaskin
Oklahoma Medical Res Foundation
Biophysical Studies on Neurofibrous Proteins in Aging
RO1 NS-19224-02; $119,287

B. Ghetti
Indiana University-Purdue University at Indianapolis
Selective Neuronal Loss and Its Sequelae: A Model
RO1 NS-14426-03; $35,105

D. Gilboe
University of Wisconsin
Metabolism of the Brain
RO1 NS-05961-17; $177,990
RO1 NS-05961-18A1; $112,594

M. Ginsberg
University of Miami
Research Center for Cerebral Vascular Disease
(10% of total award)
P50 NS-05820-18; $74,388

R. Good
Oklahoma Medical Res Foundation
Pathogenesis of CNS and Autoimmune Disorders
RO1 NS-18851-02; $147,225

I. Grundke-Iqbal
New York Institute for Basic Research
Alzheimer Neurofibrillary Pathology
RO1 NS-18105-03; $75,197

R. Hawkins
Milton S. Hershey Medical Center, Hershey, Pa.

Regional Blood-Brain Barrier Transport of Amino Acids
RO1 NS-16737-03; $115,889

R. Hogue-Angletti
University of Pennsylvania
Neurofilament Structure
RO1 NS-18362-02; $117,661

E. Holmes
Yeshiva University
Role of the Diencephalon in Memory
R23 NS-20844-01; $63,396

R. Houghten
Scripps Clinic, Lajolla, Calif.
Age-Related Changes in Endorphin Metabolism and Receptors
RO1 NS-18113-03; $103,770

R. Huang
University of South Alabama
ESR Study- Monoamine Oxidase and Membranes
RO1 NS-14434-05; $87,336

K. Iqbal
New York Institute for Basic Research
Alzheimer Neurofibrillary Tangles--Biochemical Studies
RO1 NS-17487-03; $55,067

R. Katzman
Yeshiva University
Biogenic Amines and Neurological Disorders
(10% of total award)
P50 NS-09649-12; $71,821

R. Kesner
University of Utah
Model of Alzheimer's Disease: Cholinergic Involvement
RO1 NS-19406-01; $69,444

H. Koenig
Northwestern University, Chicago
Molecular Pathology of Blood-Brain Barrier Breakdown
RO1 NS-18047-02; $106,917

G. Koob
Salk Institute for Biological Studies
Behavioral Effects of Vasopressin: Mechanism of Action
RO1 NS-18367-01A1; $74,273

D. Krause
City of Hope
Cerebrovasculature In Vitro–Neurotransmitters and Aging
RO1 NS–18586–02; $152,161

D. Kuhl
University of California, Los Angeles
Neuroscience Research Using Emission Tomography
(10% of total award)
P01 NS–15654–05; $22,501

A. Lockwood
University of Miami
PETT Studies of Cerebral Metabolism and Function
(10% of total award)
P01 NS–15639–05; $56,699

A. Lossinsky
New York State Institute, Staten Island, N.Y.
Transport Mechanisms in Altered Blood–Brain Barrier
RO1 NS–18079–02; $5,664

E. Manuelidis
Yale University
Experimental Creutzfelt–Jakob Disease (Hamsters, Mice)
R01 NS 12674–08; $143,386

R. Marsh
University of Wisconsin
Slow Infection by Unconventional Viruses (Mammals)
RO1 NS–14822–10; $137,760

M. Martinez–Maldonado
OBFS/IRP/NINCDS
Neurological Aspects of Aging in Primates
Z01 NS–02518–02; $2,666

L. Nadel
University of California, Irvine
Hippocampus and Cognition
RO1 NS–17712–03; $67,067

R. Nixon
McLean Hospital
Neurofilament Proteolysis and Alzheimer's Disease
RO1 NS–17535–03; $99,892

W. Pardridge
University of California, Los Angeles, Calif.

Neuropeptides and Blood–Brain Barrier (BBB)
RO1 NS–17701–03; $66,413

A. Pearlmutter
Medical College of Ohio, Toledo
Mechanisms of Vasopressin Action in the Brain
RO1 NS–17848–02; $79,617

F. Plum
Cornell University
Research Center in Cerebrovascular Disease
(20% of total award)
P50 NS–03346–23; 246,750

J. Posner
Sloan–Kettering, N.Y.
Positron Emission Tomography of the CNS
(10% of total award)
P01 NS–15665–05; $85,364

S. Preskorn
University of Kansas
Central Adrenergic System and Blood–Brain Barrier
RO1 NS–17252–03; $48,572

S. Prusiner
University of California, San Francisco
Multiple Sclerosis and Viral Infection of the Central Nervous System
(10% of total award)
P01 NS–14069–06; $42,615

M. Raichle
Washington University, St. Louis
An Interdisciplinary Stroke Program
(10% of total award)
P50 NS–06930–17; $60,177

T. Rainbow
University of Pennsylvania
Gonadal Steroid Effect on Neurotransmitter Receptors
R23 NS–20006–02; $56,623

M. Reivich
University of Pennsylvania
Local Cerebral Glucose Metabolism in Man
(10% of total award)
P01 NS–14867–05; $120,546

M. Reivich
University of Pennsylvania
Cerebral Blood Flow and Metabolism in Stroke and Shock
(10% of total award)
P50 NS-10939-11; $101,119

S. Roffler-Tarlov
Tufts University
Studies of Inherited Neuronal Cell Death
RO1 NS-19340-01; $108,279

P. Salvaterra
Beckman Research Institute/City of Hope
Immunological Studies of Choline Acetyltransferase
R01 NS 19482-01; $106,674

M. Sar
University of North Carolina
Hormone and Neurotransmitter Relationships in the Brain
RO1 NS-17479-02; $65,252

M. Shelanski
New York University
Pathology and Biology of Neuronal Fibrous Proteins
RO1 NS-15076-06; $183,101

R. Sidman
Children's Hospital, Boston, Mass.
Reduced Connections: Cause of Premature Neuron Aging
RO1 NS-20822-02; $173,045

D. N. Slatkin
Brookhaven National Laborabory
DNA Turnover in Human Neurons
RO1 NS-17822-02; $90,021

J. Stewart
University of Colorado
Substance P and Brain Function: Structure/Activity
RO1 NS-18531-02; $106,962

K. Suzuki
Yeshiva University
Brain Development and Developmental Neurological Disorders
(25% of total award)
P01 NS 03356-23; $179,309

J. Taveras
Massachusetts General Hospital

An Interdepartmental Stroke Program
(10% of total award)
P50 NS-10828-09; $105,853

A. Vorbrodk
New York State Institute, Staten Island, N.Y.
Microvasculature in Normal and Pathological Brain
RO1 NS-17271-03; $42,909

H. Wagner
Johns Hopkins University
Program for Study of Neuroreceptor Binding in Man
(10% of total award)
P01 NS-15080-05; $52,584

B. Weiss
Medical College of Pennsylvania
Regulation of Brain Aminergic Receptors in Aging
RO1 NS-16242-03; $115,388

D. D. Wheeler
Medical University of South Carolina
Aging, Transport, and Synaptic Function in the CNS
RO1 NS-12292-08; $75,712

A. Wolf
Brookhaven National Laboratory
Radiotracer B and D in Nuclear Medicine and Neuroscience
(10% of total award)
RO1 NS-15380-08; $29,132

A. Wolf
Brookhaven National Laboratory
Positron Emitters and PETT in Metabolic and Neurological Science
(10% of total award)
P01 NS-15638-05; $142,000

R. Zackroff
Northwestern University
Characterization of Neural Intermediate Filaments
R23 NS-18675-02; $51,884

3. Diagnosis

P. Fedio
CN/IRP/NINCDS
Cognitive and Emotional Profile of Neuropsychiatric Disorders
Z01 NS-00200-28; $111,300

P. Fedio
CN/IRP/NINCDS
EEG Learning Correlates Using Scalp and Intracranial Depth Electrodes
Z01 NS-01245-17; $130,941

M. Folstein
Johns Hopkins University, Baltimore, Md.
Research Center Without Walls for Huntington's Disease
(50% of total award)
P01 NS-16375-04; $259,150

P. Fuld
Yeshiva University
Behavioral Differentiation of the Dementias
RO1 NS-18248-01A1; $52,181

J. Martin
Massachusetts General Hospital
Research Center Without Walls for Huntington's Disease
(50% of total award)
P50 NS-16367-04; $371,969
P50 NS-16367-04S1; $18,227

A. Pikus
CDP/CD/NINCDS
Audiologic Findings in an Aging Population
Z01 NS-02470-03; $8,639

A. Pikus
CDP/CD/NINCDS
Audiologic Findings in Alzheimer's Disease
Z01 NS-02559-02; $4,320

A. Pikus
CDP/CD/NINCDS
Audiologic Findings in Twins with Alzheimer's Disease
Z01 NS-02556-01; $4,320

4. Clinical Course

R. Katzman
Yeshiva University
Senile Dementia: Prospective Study of Risks and Course
P01 NS-19234-01; $577,559

5. Treatment

(See 4, R. Katzman- physostigmine and lecithin therapy)

8. Training of Research and Clinical Personnel

The NINCDS currently supports the following numbers of trainees at the total funding levels indicated: NRSA institutional grants (training grants), 336 trainees, $5,353,000; NRSA individual post-doctoral fellow, 240 trainees, $4,336,000. The NINCDS also sponsors two manpower programs that are designed to aid in the development of basic researchers (RCDA) and clinical investigators (TIDA) into mature scientists. The RCDA supports 58 young basic scientists at a level of $2,225,000, while the TIDA supports 118 young physicians for $5,034,000. The areas addressed by these scientists include Alzheimer's disease. The funding of these programs totals $16,948,000.

9. Educational Materials and Information Dissemination

An active dissemination-of-information program in Alzheimer's disease is carried out by the NINCDS. This Institute has two publications that provide up-to-date information about Alzheimer's disease: *The Dementias: Hope Through Research*, and *Alzheimer's Disease: A Scientific Guide for Health Practitioners*. The effort has also included the editing of the seminal volume on this disorder: *Alzheimer's Disease: Senile Dementia and Related Disorders*, which is a source book for researchers and clinicians in this field.

Veterans Administration Grants Relating to Alzheimer's Disease

Active as of October 31, 1983

1. Epidemiology

L. M. Schuman, M.D.
Minneapolis VAMC
Epidemiologic Study of Alzheimer's Disease

2. Etiology and Pathogenesis

Thomas Bird, M.D.
Seattle VAMC
Neurochemical Mechanisms in Dementia and Hereditary Neurologic Disorders

Stephen De Armond, M.D., Ph.D.
Palo Alto VAMC
Correlated Biochemical and Electronic Microscopic Autoradiographic Study of GFA Protein and Glial Filament Metabolism

Jeffrey Halter, M.D.
Seattle VAMC
Aging and Sympathetic Nervous System Dysfunction

John Peacock, M.D., Ph.D.
Reno VAMC
Electrophysiology of Hippocampal Granule Cell Cultures

Govindankutty Vattassery, Ph.D.
Minneapolis VAMC
Vitamin E and Other Antioxidants in Aged and Pathological Brains

Ladislav Volicer, M.D., Ph.D.
Beford VAMC
Changes of Superoxide Dismutase in Patients with Alzheimer's Disease

3. Diagnosis

Marilyn Albert, Ph.D.
Boston VAMC
Retrograde Amnesia in Alcohol and Non-Alcohol Related Dementias

Martin Albert, M.D.
Boston VAMC
Language in the Aging Brain

Claude Baxter, Ph.D.
Sepulveda VAMC
Nervous System Regulatory Processes Involving Amino Acids and Proteins

Nelson Butters, Ph.D.
Boston VAMC
Cognitive Processes After Brain Damage

Cermak Laird, Ph.D.
Boston VAMC
Neuropsychology of Information Processing and Memory

Kenneth Davis, M.D.
Bronx VAMC
Cerebrospinal Fluid Studies in Senile Dementia and Age Matched Controls

Lorne Direnfeld, M.D.
Boston VAMC
Dementia in Parkinson's Disease

Robert Dustman, Ph.D.
Salt Lake City VAMC
Electrophysiological and Behavioral Indices of Aging and Development

Irwin Feinberg, M.D.
San Francisco VAMC
Biopsychological Implications of Changes in Sleep Patterns with Age

Robert Friedland, M.D.
Martinez VAMC
Cerebral Metabolic Indices of Dementia Pathophysiology

John Hutton, M.D.
Lubbock VAMC
Neurological Aspects of Visual Tracking in Dementia

Michael Malone, M.D.
Bedford VAMC
Senile Dementia: Neurochemical Studies

William Markensberg, M.D.
Lexington VAMC
Growth Characteristics of Cultured Fibroblasts from Patients with Alzheimer's Disease

William Markesberg, M.D.
Lexington VAMC
Trace Element Content of CNS in Aging

William Milbereg, Ph.D.
Boston VAMC
Cognitive Deficit Identification in Dementia

Richard Mohs, Ph.D.
Bronx VAMC
Aging and Alzheimer's Disease: Cognitive Studies

Gerald Morley, M.D.
Minneapolis VAMC
Longitudinal Study of Memory Processes in Presenile and Senile Dementia

James Mortimer, Ph.D., and David Webster, M.D.
Minneapolis VAMC
Interrelationship of Motor Cognitive Function in Aging and Disease

Nandy Kalidas, Ph.D.
Bedford VAMC
Brain-Reactive Antibodies in Aging

Adolf Pfefferbaum, M.D.
Palo Alto VAMC
The P300 Event-Related Brain Potential in the Diagnosis of Dementia

Patricia Prinz, Ph.D.
American Lake VAMC
Sleep-Waking Patterns in Dementia

Patricia Randels, M.D.
Coatesville VAMC
Biological Markers in Alzheimer's Disease

Constance Ray, Ph.D.
Bedford VAMC

Electrophysiological Assessment of Association Cortex in Dementia

Walter Reige, Ph.D.
Sepulveda VAMC
Multivariant Assessment of Memory Functions in Aged and the Alcoholic

Benjamin Selzter, M.D.
Bedford VAMC
Cortical Connections and Neurobehavioral Disorders

Steven Sevush, M.D.
Miami VAMC
Attention Factors in Language Comprehension

Larry Squire, Ph.D.
San Diego VAMC
The Neuropsychology of Memory

Charles Watson, Ph.D.
St. Cloud VAMC
Psychological Characteristics of Alzheimer's and Senile Dementia

Christopher West, Ph.D.
Bedford VAMC
Dietary Restriction and Aging Brain

4. Clinical Course

Marilyn Albert, Ph.D.
Boston VAMC
Age Related Changes of Cognition in Health and Disease

Moira Breen, Ph.D.
North Chicago VAMC
Proteoglycans in the Normal Lung and Brain as a Function of Age

Steven Dekosky, M.D.
Lexington VAMC
Microchemical Alterations in Aging and Dementia: Cortex and Hippocampus

Lysia Forno, M.D.
Palo Alto VAMC
Structural Changes in Parkinsonism and Related Disorders

Terry Jernigan, Ph.D.
Palo Alto VAMC

Neurobehavioral Relations in Aging, Alcoholism, Dementia, and Schizophrenia

Bert Kopell, Ph.D.
Palo Alto VAMC
Event-Related Potentials: Basic and Clinical Investigations

David Masuoka, Ph.D.
Sepulveda VAMC
Age Related Changes in Monoaminergic Neurons of the CNS

Murray Raskind, M.D.
Seattle VAMC
Secondary Depression in Senile Dementia of the Alzheimer's Type

P. Bart Vrtunski, Ph.D.
Cleveland VAMC
Microbehavioral Analysis of Psychomotor Decrements in Aging Veterans

Leslie Zatz, M.D.
Palo Alto VAMC
Studies on CCT: Aging, Dementia, Alcoholism and Schizophrenia

5. Treatment

Burton Angrist, M.D.
New York VAMC
A Controlled Assessment of CCK-8 in Schizophrenia and Cognitive Impairment

Arthur Cherkin, Ph.D.
Sepulveda VAMC
Enhancement of Memory Processes Relevant to Aging

Joel Davis, Ph.D.
Sepulveda VAMC
Proline Neuropeptide Influences on Age-Related Memory Processes

Kenneth Davis, M.D.
Bronx VAMC
A Cholinergic Basis for Rational Treatment of Memory Deficits in the Aged

Kenneth Davis, M.D.
Bronx VAMC
Lecithin and Piracetam in Patients with Alzheimer's Disease

John Meyer, M.D.
Durham VAMC
Aging, TIAs, Strokes, Dementia: Natural History, Prevention, Trials of Treatment

David Osborne, M.D.
New York VAMC
Memory Enhancement in Aging

Yvette Rheaume, R.N., B.S.N.
Bedford VAMC
Effects of Pacing on Physical Health of Progressive Dementia Patients

Michael Serby, M.D.
New York VAMC
A Double Blind Study of Piracetam and Lecithin in Alzheimer's Disease

Thomas Walshe, M.D.
Brockton VAMC
A Trial of Propranolol in the Treatment of Aggressive Behavior in Patients with Dementia

Jerome Yesavage, M.D.
Palo Alto VAMC
Treatment of Senile Dementia

6. The Family

Lissy Jarvik, M.D., Ph.D.
Brentwood VAMC
Family Study of Alzheimer's Dementia

7. Systems of Care

The extended care system within the VA provides a range of services important in meeting the complex needs of the Alzheimer's patient. This includes not only acute care within a VA medical center but also a range of comprehensive services available in some of the VA's 99 Nursing Homes, 43 Hospital-Based Home Care Programs, 9 Geriatric Evaluation Units, and 5 Adult Day Health Care Centers. VA patients with Alzheimer's disease may also receive care in State Homes receiving funding either through the VA's per diem program or its construction program.

VA Nursing Home Care

The nursing home care units located in 99 VA medical centers provide skilled nursing care and related medical services as well as opportunities for social, diversional, recreational, and spiritual activities. Nursing home care patients frequently require a prolonged period of care and supervision.

Community Nursing Home Care

This is a contract program for veterans who require skilled or intermediate nursing care in making the transition from a hospital to a community. The program requires assessment of participating facilities and followup visits to veterans by teams from the VA medical centers. In Fiscal Year 1982, some 3,100 community nursing homes were under contract with the VA.

VA Domiciliary Care

Domiciliary care in 16 facilities provides necessary medical and other professional care for eligible ambulatory veterans who are disabled by age, disease, or injury and are in need of care but do not require hospitalization or the skilled services of a nursing home. There is an increasing emphasis on rehabilitation.

VA domiciliaries are located at Bath, New York; Martinsburg, West Virginia; Hampton, Virginia; Mountain Home, Tennessee; Dublin, Georgia; Biloxi, Mississippi; Bay Pines, Florida; Dayton, Ohio; Wood, Wisconsin; Bonham and Temple, Texas; Leavenworth, Kansas; Hot Springs, South Dakota; Prescott, Arizona; Los Angeles, California; and White City, Oregon.

Hospital-Based Home Care

There are currently 43 hospital-based home care programs in the VA. This program arranges for selected patients who would otherwise remain in the hospital to return to their own homes for further care. The patient and the family are provided instruction in nursing procedures and in daily care under the coordinated supervision of a hospital-based treatment team. The team provides medical, nursing, social, rehabilitation, and dietetic regimens as followup to hospital care.

Geriatric Evaluation Units (GEUs)

Nine VA facilities have established GEUs, and 15 more have indicated their interest in doing so. The goal of a GEU is to improve the diagnosis, treatment, and placement of older patients using an interdisciplinary team approach.

GEUs established to date include those at Memphis and Knoxville, Tennessee; Houston and Temple, Texas; West Roxbury, Massachusetts; Minneapolis, Minnesota; Coatesville, Pennsylvania.; Hampton, Virginia; and Sepulveda, California.

Adult (Geriatric) Day Health Care

Adult (geriatric) day health-care centers provide health maintenance and therapeutic activities in a congregate setting for veterans who, without the program, would require continued and full-time institutionalization. Program models are in operation at five VA medical centers--North Chicago, Illinois; Loma Linda, California; American Lake, Washington; Palo Alto, California; and Boston OPC, Massachusetts.

8. Training of Research and Clinical Personnel

Medical and Dental Students, Housestaff, and Allied Health

The VA medical care system has grown to encompass 172 VA medical centers and 220 outpatient clinics serving over 3 million individual veterans; 1,015 educational institutions are affiliated with VA medical centers. These affiliations cover 2,230 health occupations programs providing training for students in approximately 30 disciplines. Many of these trainees care for VA patients with Alzheimer's disease.

Fellowship Programs

In response to both specific needs unique to the care of the veteran patients and vastly increased requirements for care, the Office of Academic Affairs has developed a series of 2-year fellowship programs in the fields of geriatrics, spinal cord injury, and substance abuse. The VA also participates in the Robert Wood Johnson Clinical Scholars Program

The 2-year fellowships were started in 1978. As of June 1984, 79 Geriatric Fellows will have graduated from the Geriatric Fellowship Program.

Veterans, including the large group from WW II, are a significant sample of the general population whose aging will create unique problems and challenges in the next 20 years. This includes the veteran with Alzheimer's disease.

Nurse Scholarship Program

The need to assist the training of specific types of health care practitioners prompted the Congress to enact, in Public Law 96-330, the VA Health Professionals Scholarship Program. In 1982, the $6 million earmarked for the program was invested in 344 scholarship awards to nursing students in both baccalaureate and masters degree programs. Special emphasis was given to VA employees and to those enrolled in masters programs in clinical areas needed by veteran patients. In the future, support of VA employees attending nursing schools part time will become a part of the program. Many of these students provide care to the patient with Alzheimer's disease.

VA Continuing Education

Education and training within the Veterans Administration extends beyond the training of students seeking a degree or certificate. Continuing education is accomplished not only by sending employees to educational programs sponsored by professional, educational, and other organizations but also by maintaining with the VA itself a large and responsive continuing education operation. This in-house activity involves programing within all the individual VA hospitals as well as a network of continuing education field units--seven Regional Medical Education Centers (RMECs) located throughout the country to provide educational programing on a regional basis, a Continuing Education Center (CEC) in Washington, D.C., to design and coordinate nationwide programs; two Dental Education Centers (DECs), and one Engineering Training Center (ETC). Libraries, medical media, television production studios, education specialists, and curriculum designers all play important roles in accomplishing the continuing education mission. In addition to these centers for continuing education, the VA is a partner in eight Cooperative Health Manpower Education Programs (CHEPs). An outgrowth of the Area Health Education Centers (AHECs) of the 1970s, CHEPs are associated with remote area VA medical centers which do not have formal medical school affiliations. These programs assist in both health manpower production and continuing education in their immediate service areas. Each CHEP has a unique organization and a consortium relationship structured to meet local educational needs. An increasing number of continuing education programs cover Alzheimer's disease.

Geriatric Education and Training

GRECC. In another response to the needs of older veterans, the VA, in concert with the Congress, has developed a number of Geriatric Research, Education and Clinical Centers (GRECCs).

The GRECC program consists of 10 centers hosted by VA medical centers and represents an important response to the health care needs of aging veterans. GRECCs serve to utilize and redirect resources for geriatric care and to advance and integrate research and educational achievements in geriatrics and gerontology into the VA health care system. GEUs and geriatric rehabilitation units consisting of from 10 to 30 beds have been activated at the GRECCs for intensive diagosis, research, and therapy.

These GEUs are currently under study, as are other models of geriatric and extended care service delivery. The clinical foci include drug metabolism, geropsychiatry, nutrition, team care, cardiopulmonary rehabilitation, endocrinology, and various dementias including Alzheimer's disease. GRECCs are located at Boston (Brockton/West Roxbury and Bedford Divisions), Durham, Gainesville, Little Rock, Minneapolis, Palo Alto, St. Louis, Seattle (including the Seattle and American Lake Divisions), Sepulveda, and West Los Angeles.

ITTG. Model Interdisciplinary Team Training in Geriatrics (ITTG) has been developed at 12 sites: Birmingham, Alabama;

Buffalo, New York; Coatesville, Pennsylvania; Little Rock, Arkansas; Madison, Wisconsin; Memphis, Tennessee; Palo Alto, California; Portland, Oregon; Salt Lake City, Utah; Sepulveda, California; Tampa, Florida; and Tucson, Arizona. These teams allow the blending of specialized skills contributed by each member of the team to aid in meeting the complex needs of the older veteran who characteristically has multisystem disease and requires both medical care and social support services. Teams such as these are able to provide highly skilled care to Alzheimer's patients.

NOTE: The primary sources for this material on VA grants are the following documents:

1. *Administrator of Veterans Affairs Annual Report 1982.*

2. Worthen, David M. "Health Professions Education and Training Within the Veterans Administration," revised October 5, 1983, from an earlier paper by the same author entitled "Programs Become National Resources," *U.S. Medicine,* August 1, 1983.

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